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## ORIGINAL ARTICLES

# THE UNRELIABILITY OF CYANOSIS IN THE RECOGNITION OF ARTERIAL ANOXEMIA*

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In 1919 Stadie[7] first correlated arterial oxygen saturations with clinical impressions of cyanosis in patients with pneumonia. His data show that lower arterial oxygen saturations were usually associated with more intense cyanosis but that the arterial saturations corresponding to impressions of slight, moderate, marked and intense cyanosis varied widely in different patients. In 12 patients with "moderate cyanosis," the arterial oxygen saturations ranged from 65 to 91% while in 12 instances of "marked cyanosis," the saturations varied from 56 to 86%. A few years later, Lundsgaard and Van Slyke,[5] in their monograph, "Cyanosis," summarized the factors which contribute to the presence of cyanosis and concluded that approximately 5 gm. of reduced hemoglobin must be present in 100 cc. of capillary blood to produce visible cyanosis in an individual otherwise normal; this could correspond to an arterial oxygen saturation of 80% and a venous saturation of 55% (assuming a peripheral A–V oxygen difference of 5 vols. per 100 cc.). An arterial oxygen saturation of 80% is equivalent to that produced by inhalation of 10 to 12% oxygen instead of the normal 21% present in room air.

Despite these 2 careful studies which indicated that serious arterial anoxemia may exist before even moderate cyanosis is visible, most physicians have continued to regard cyanosis as the most characteristic sign of anoxemia and the most reliable guide for intelligent oxygen therapy.[2] It has been our impression for some years that excellent diagnosticians differ widely in their ability to recognize visually the presence of arterial anoxemia. The development of the oximeter by Millikan[6] provided us with a new method with which we could repeat and extend earlier studies[7] using large numbers of observers and subjects. It became evident early in these studies (*a*) that the detection of cyanosis depends not only upon variables in the *patient*,[1,5] but also upon variables in observers and (*b*) that cyanosis is a poor guide for the detection of arterial anoxemia of slight to moderate degrees.

* This work was performed under contract with the Medical Division, Chemical Warfare Service, Edgewood Arsenal, Maryland.

**Method.** These experiments were designed to measure the highest arterial oxygen saturation at which observers could detect cyanosis. The arterial oxygen saturation of normal subjects was varied by the inhalation of low oxygen mixtures while observers attempted to estimate the existence and degree of cyanosis present. The arterial oxygen saturation was measured continuously by an oximeter. This instrument is essentially a miniature photo-electric colorimeter which may be placed on the ear; it measures arterial oxygen saturation with an average accuracy of 3% (as compared with values obtained by direct determinations on arterial blood). A total of 20 subjects (normal white males between the ages of 19 and 25, all accustomed to laboratory procedures) and 127 observers (105 medical students and 22 physicians) participated in the study.

A typical experiment was conducted as follows: An oximeter was attached to the subject's left ear. His nose was occluded by a clip. He then breathed through a mouthpiece, an inspiratory demand valve, and an expiratory flutter valve. Arrangements were made so that he might inhale room air, 100% oxygen, or 12, 10, or 8% oxygen (the remainder of the gas mixture in the latter 3 instances being nitrogen) in random sequence; precautions were taken that no one except the recorder knew the gas mixture being inhaled or the oximeter readings until the experiment was concluded. Five 6000 liter high pressure tanks containing the gas mixtures were connected to a 5 outlet manifold; the oximeter recorder, the gas tanks and all manipulations of these were obscured from the observers and subject by a screen. The subject was given room air to breathe, and the observers were informed that the subject's color at that moment represented his "normal" color.* From this time on the observers, in groups of 4 to 10, were instructed to note the color of the subject's face, right ear, hands, fingers or nail-beds every ½ minute and independently record it as "normal," "slightly or questionably cyanotic" or "definitely cyanotic." Since each experiment lasted approximately 30 minutes, each observer made about 60 color estimations. During this time the subject was given high and some of the low oxygen atmospheres to breathe for variable periods of time. Each subject was made anoxemic at least twice in each experiment. Each low oxygen mixture was breathed for a minimum of 2 minutes after the oximeter had reached its lowest level.

The conditions under which the experiments were conducted were unusually favorable for early detection of cyanosis by the observer for several reasons: (*a*) the experimental room was lighted by daylight or by artificial tungsten filament lamps; (*b*) the subject's normal color was observed as a control with which ensuing color changes could be compared; (*c*) the observers were informed that periods of low and high arterial oxygen saturation in the subject could be expected during the ensuing 30 minute period; and (*d*) all subjects were white males.

The studies were conducted in a warm room, free from draughts, to minimize the occurrence of peripheral vasoconstriction and local cyanosis due to cold. Total hemoglobin was determined upon venous blood in 16 of 20 subjects; hemoglobin varied from 13.5 to 16.5 gm. per 100 cc.

**Results.** In Table 1 are recorded the levels of arterial oxygen saturation corresponding to estimations of "normal color," "slight or questionable cyanosis" and "definite cyanosis." This shows that the visual impressions of cyanosis are not necessarily accurate indications of anoxemia. Of the 3673 observations made when the subjects were breathing room air or oxygen and had oximeter readings of 96 to 100%, 26% stated that slight cyanosis existed. Furthermore only 49% of the students and 53% of the staff observations indicated "definite cyanosis" at the times when the oximeter registered 81 to 85% saturation (the level found by Stadie in severe lobar pneumonia).[7] Even at 71 to 75% saturation, 25% of the student and 15% of the staff observations recorded only "slight cyanosis."

The *highest* level of arterial oxygen

* When the medical students acted as observers, a trial experiment was conducted first: The subject breathed 8 or 10% oxygen and the observers watched the development of cyanosis while the recorder called out the oximeter readings. When all observers recognized definite cyanosis, the subject breathed 100% oxygen and the observers were thus permitted to observe the abrupt color change from blue to pink.

saturation at which each observer noted definite cyanosis is recorded in Table 2. Because of the marked inconsistencies that occurred in the records of many observers, data from consistent "series" only are included in this table.* The median in both the student and staff groups noted definite cyanosis at 85 to 81% saturation. For example, 1 physician first noted definite cyanosis at levels of 84, 77, 94 and 82% in 4 consecutive trials upon the same subject within a period of 40 minutes. There were 35 cases in which observers noted definite cyanosis (in consistent series) 2 to 5 times in the same subject. In 11 instances (31%) the highest and lowest levels at which the observer first noted cyanosis varied by 5% saturation or less, and in 13 of the other 24 instances the variation was 10% saturation or more. The highest and lowest levels at which definite cyanosis was first noted could not be determined accurately in all of the experiments. However, 20 observers (see Table 2) did not detect definite cyanosis until the oximeter readings fell below 75% saturation. On the other hand, 11 observers noted (in "consistent series") definite cyanosis at saturations above 90%. The validity of the observations at the higher levels may be questioned since none of the sudden "switchbacks" to 100% $O_2$ occurred when the saturations were above 90%; hence these observations were not so rigidly controlled as those in the 70 to 90% range, in which the ability to

TABLE 1.—PERCENTAGES OF TOTAL OBSERVATIONS AT VARIOUS ARTERIAL OXYGEN SATURATION LEVELS NOTED AS NORMAL COLOR, SLIGHT CYANOSIS OR DEFINITE CYANOSIS

| Oximeter reading (arterial $O_2$ saturation) | No. observations at each arterial $O_2$ level | | | % observations reported | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Normal color | | | Slight cyanosis | | | Definite cyanosis | | |
| | Students | Staff | Total | Students (%) | Staff (%) | Total (%) | Students (%) | Staff (%) | Total (%) | Students (%) | Staff (%) | Total (%) |
| 100-96 | 2865 | 808 | 3673 | 67 | 70 | 68 | 27 | 22 | 26 | 6 | 8 | 6 |
| 95-91 | 711 | 203 | 914 | 42 | 48 | 43 | 42 | 32 | 40 | 16 | 20 | 17 |
| 90-86 | 712 | 182 | 894 | 33 | 25 | 32 | 36 | 43 | 37 | 31 | 32 | 31 |
| 85-81 | 799 | 244 | 1043 | 15 | 10 | 14 | 36 | 37 | 37 | 49 | 53 | 49 |
| 80-76 | 418 | 76 | 494 | 10 | 4 | 10 | 43 | 29 | 40 | 47 | 67 | 50 |
| 75-71 | 139 | 47 | 186 | 4 | 0 | 3 | 25 | 15 | 22 | 71 | 85 | 75 |
| Total | 5644 | 1560 | 7204 | | | | | | | | | |

TABLE 2.—HIGHEST LEVEL OF ARTERIAL OXYGEN SATURATION AT WHICH DEFINITE CYANOSIS WAS NOTED BY EACH OBSERVER WHO MADE 1 OR MORE SERIES OF CONSISTENT OBSERVATIONS.

| Oximeter reading (arterial $O_2$ saturation) | Students | Staff | Total |
|---|---|---|---|
| 100-96 | 1 | .. | 1 |
| 95-91 | 9 | 2 | 11 |
| 90-86 | 15 | 5 | 20 |
| 85-81 | 19 | 7 | 26 |
| 80-76 | 9 | 2 | 11 |
| 75 or below | 18 | 2 | 20 |
| | 71 | 18 | 89 |

It must be remembered that the data in Table 2 represent the *highest* saturations at which observers detected definite cyanosis. An observer often noted cyanosis at a high level in 1 series of observations and 10 to 20 minutes later was unable to detect cyanosis in the same subject until a much lower oximeter reading was reached.

* A "series" is defined as the observations during a consecutive sequence of high oxygen, low oxygen and high oxygen inhalation. "Consistency" of an observer for a series was judged by the following criteria: (*a*) the observer must have noted "normal color" throughout the period that the subject was breathing room air or 100% $O_2$; (*b*) if the observer recorded slight or definite cyanosis at some time after the subject inhaled a low oxygen mixture and the oximeter reading started to fall, he must have consistently recorded cyanosis until the subject breathed a mixture richer in oxygen and the oximeter readings rose; and (*c*) the observer must have noted later in the same experiment an abrupt change from "cyanosis" to "normal color" within 1 minute after the subject suddenly breathed 100% $O_2$ (following 12, 10, or 8% oxygen) and the oximeter readings rose to 95% or more.

note a sudden change from cyanosis to normal color aided in determining the "consistency" of each series.

There were also marked variations in the ability of different observers to detect cyanosis in any one subject. One observer noted definite cyanosis at a level of 94% saturation while a second physician, observing the same subject simultaneously, could not detect definite cyanosis until the oximeter fell to 71%, a difference of 23%. Differences of this type were noted in observations made upon each of the 20 subjects; these ranged from 3 to 23% (median 12%).

Though all the subjects were white males, cyanosis was not detected at the same level in all. It is impossible to state the average level at which cyanosis was observed in the different subjects, since some observers did not detect cyanosis at the lowest level of oxygen saturation reached in each series. It was evident though that the majority of observers could detect cyanosis at a level of 85% saturation or more in some subjects, but not until a level of 75% saturation or less in others. More quantitative information is available from an analysis of the number of "consistent series" noted in each subject. Upon 1 subject,. no consistent observations were made by 7 observers (2 series each); in another, 11 "consistent series" were recorded by 7 observers out of a total of 14 series. In 4 subjects, 25% or less of the series were consistent; in 3, more than 50% of the series were "consistent." Our data indicate that few physicians make consistent observations on every trial. Of those observers who participated in only 2 series, 23% were consistent in both, of those in 3 series, 20% were consistent in all 3, in 4, only 13% were consistent throughout, while of those who had 5 trials, no observer was consistent in all.

The value of the notation "slightly cyanotic" is questionable for the following reason: 55% of 255 series of observations by medical students and 53% of 89 series by physicians were "inconsistent." The most frequent inconsistency was in criterion "a" (see page 3); when the subjects were breathing room air or 100% $O_2$, observers noted slight (usually) or definite cyanosis in 44% of the series.

Repeated practice by 1 individual in observing cyanosis over a period of 1 month did not enable her to detect definite cyanosis at higher levels of oxygen saturation or to become more consistent in her observations. Furthermore, those observers who participated in many trials were not significantly more consistent than those who participated in only 2, and the physicians as a group were no more consistent or able observers than were the inexperienced students.

There was no correlation in these experiments between the subject's total hemoglobin and the ability of observers to detect cyanosis early or consistently. However, no anemic or polycythemic subjects were included in this study (all the hemoglobins were above 13.5 and below 16.5 gm. per 100 cc.).

**Discussion.** Lundsgaard and Van Slyke[5] defined cyanosis as the blueness of the skin, mucous membranes or organs caused by changes in capillary blood (usually the presence of unusual amounts of reduced hemoglobin). In their opinion the most important factors which modify the perception of cyanosis are; (*a*) the thickness, color and opacity of the skin or membrane overlying the capillaries, (*b*) the number and length of blood filled capillaries in a given surface area, and the state of dilatation or constriction of the arterioles, capillaries or venules under observation, (*c*) variations in plasma color caused by dyes or drugs, and (*d*) variations in the type, color and amount of hemoglobin (presence of methemoglobin, sulfhemoglobin or carboxyhemoglobin).

The factors mentioned by Lundsgaard and Van Slyke are concerned with variables in the patient. We believe that an equally important variable is the wide range in the abilities of observers to detect cyanosis in any one patient. On the basis of our experiments, we can infer that very few physicians are capable of detecting slight degrees of arterial anox-

emia by the perception of surface blueness. It is probable that an extremely small percentage of physicians could be expected to diagnose early cyanosis in every case. In the majority of cases, arterial anoxemia is probably unrecognized until the saturation of hemoglobin with oxygen has fallen below 85%; in some it is unrecognized even at the 70 to 75% level.

It may be argued by those physicians who consider themselves highly skilled in the detection of cyanosis that most of our observers were relatively inexperienced medical students. It should be emphasized that the students had a preliminary trial in order to acquaint them with the color to be expected at each level of oxygen saturation in the particular subject under observation. Actually the students were only slightly less consistent in their estimations than was the physician group, which included physician anesthesiologists, and cardiologists who had wide experience in the detection of cyanosis. Furthermore the median observers noted definite cyanosis at the same level in both groups. In addition, conditions were particularly favorable for the recognition and recording of cyanosis at high levels of arterial oxygen saturation: the presence of good lighting, the opportunity to observe normal control color in each subject, the use of all young white male subjects, the awareness that a color change was imminent, and the use of a continuous method of measuring oxygen saturation, so that better correlation was obtained.

Another possible criticism of these experiments is that oximeter readings were employed instead of actual figures obtained by direct analysis of arterial blood. The oximeter has an average error of 3%; in the saturation range 75 to 100%, the limit of error is 5% and in the range 50 to 75% it is 8%. However, this error is not a systematically high or low one and should cancel out in a large series of observations. The oximeter has the advantage of continuous recording so that the saturation of arterial blood can be known at the instant that cyanosis is recorded; this favors the recording of cyanosis at higher levels of arterial saturation.

It should be emphasized that not only is cyanosis frequently an unreliable guide to slight to moderate arterial anoxemia, but also other commonly used signs, such as rapid pulse and hyperpnea are not trustworthy. Dripps and Comroe studied the effects of breathing low oxygen mixtures for 8 minutes upon the circulation and respiration of normal subjects. They found that the inhalation of 18% $O_2$ led to an average increase in pulse rate of only 4%, 16% $O_2$ to 8% increase, 14% $O_2$ to 6% increase, 12% $O_2$ to 16% increase and 10% $O_2$ to 30% increase. These low oxygen mixtures corresponded to average arterial oxygen saturations of 94, 91, 89, 81 and 73% respectively. In the same experiments[4] respiration was not increased measurably by arterial anoxemia until 10% $O_2$ was inhaled. At this point, respiratory minute volume increased only 16% (average arterial saturation 73%). Although data obtained from such brief exposures to low oxygen concentrations do not necessarily apply to clinical anoxemia, they suggest that slight anoxemia produces effects upon circulation and respiration which could escape even careful clinical observations. In some individuals the respiratory and circulatory responses are absent or poor even with moderate degrees of anoxemia.

Although other signs (mental confusion, delirium) have been suggested as indications for oxygen therapy, they do not represent early changes. In our experience, the extent of arterial anoxemia can be determined accurately in patients only by direct analyses of arterial blood.*

* The oximeter at present cannot be employed to indicate the level of arterial oxygen saturation in cyanotic individuals since the instrument must be "set" for each individual at a *known* value. In an individual known to be normal, the oximeter is "set" at 95 to 98% if the individual is breathing room air or at 100% if breathing oxygen. In a cyanotic patient, an arterial puncture can be performed, a determination of oxygen saturation can be done quickly by the method of the Van Slyke and Neill,[5] and the oximeter can then be "set" to this figure. An evaluation of therapy can then be made easily by noting oximeter changes in response to the employment of oxygen by oropharyngeal catheter, tent, mask or by pressure breathing.

Furthermore, our data indicate that this is the only way in which slight to moderate degree of anoxemia can be detected.

In present practice of medicine, every effort is being made to place therapy upon a scientific basis. It is often essential to know blood sulfonamide, penicillin and salicylate levels in order properly to evaluate therapy. Yet in the evaluation of arterial anoxemia, the clinician still uses a relatively insensitive and unreliable guide, namely cyanosis. The methods for determining arterial oxygen concentration are well established. Arterial puncture is neither dangerous nor painful if done carefully. It is suggested that oxygen therapy be put upon a more quantitative basis by measuring arterial saturation in patients suspected of being anoxemic and by employing doses or concentrations of oxygen sufficient to increase arterial saturation to normal levels. More frequent measurements of arterial oxygen saturation by direct means (in patients suspected of being anoxemic) should result in the elimination of much unnecessary oxygen therapy. It will also result frequently in the correction of concentrations of oxygen being given to those in need of oxygen.

Oxygen therapy is of value in many cases of anoxemia. The patient who is chronically anoxemic usually develops certain compensatory changes which permit a relatively normal existence at rest without the need for oxygen administration. However, the recovery of an *acutely* anoxemic patient (who often has fever and accelerated metabolism) can be hastened by maintaining normal amounts of oxygen in the blood. It is doubtful if oxygen therapy *per se* cures disease processes. However, it is of great value as supportive therapy in anoxemia and there it should be used more quantitatively. When oxygen is given in high concentrations in the treatment of conditions unassociated with anoxemia[3] (*e. g.*, in coronary occlusion, etc.), determinations of arterial oxygen saturation are unnecessary since the arterial blood is almost completely saturated before oxygen inhalation is begun.

**Summary and Conclusions.** 1. The ability of observers to detect cyanosis was evaluated by comparing their color estimations with known arterial oxygen saturations (oximeter).

2. The majority of 127 observers were unable to detect the presence of definite cyanosis until the arterial oxygen saturation fell to approximately 80%; 25% of observers did not note definite cyanosis even at arterial saturation levels of 71 to 75%.

3. There were marked variations in the ability of an observer to note cyanosis in different subjects or even in the same subject at different times. There were wide variations in color estimations when 5 to 10 observers watched cyanosis develop in the same subject at the same time.

4. The detection of cyanosis is dependent not only upon variable factors in the patient but also upon the ability of individual observers to note color changes.

5. Visual impressions of cyanosis are unreliable. Serious grades of arterial anoxemia may be unrecognized by many physicians unless arterial blood is obtained and analyzed for oxygen content and capacity.

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# PHLEBOGRAPHY FOR THE STUDY OF OBSTRUCTION OF THE VEINS OF THE SUPERIOR VENA CAVAL SYSTEM*

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Phlebography, by providing Roentgen visualization of the veins, offers a method unequalled by other techniques for defining and localizing lesions of the veins and determining the distribution of the collateral circulation. This method has been used mainly in connection with thrombosis of the veins of the lower extremity. Its importance in similar lesions of the veins of the superior vena caval system has not been emphasized. Some reports on diseases of the superior vena cava[4] and of the subclavian and axillary veins[7,8] have included phlebographic studies. There has been no report which offers a full appraisal of the value and limitations of phlebography in cases of obstruction of the superior vena cava and its main tributaries. It is our purpose, therefore, to present cases which are illustrative of our experience in lesions of this type, and which provide adequate testimony to the value of phlebography as a means for precise diagnosis.

**Technique.** The technique of phlebography in the superior vena caval system is quite simple. The sites usually employed for injection of the contrast medium are the external jugular vein and the median basilic vein. For lesions of the superior vena cava or innominate vein, the external jugular is preferred, although when this vein is not accessible, the veins of the antecubital fossa may be used. In lesions of the subclavian, axillary, or brachial veins, the median basilic is selected. Use of other veins in the antecubital fossa, particularly the cephalic, may lead to errors in interpretation when the obstruction occurs solely in the axillary or brachial veins. This is made obvious by reference to Figure 8. The cephalic vein enters the axillary vein at a point close to the subclavian, so that obstruction in the axillary or brachial vein will not be visualized.

The materials we have used for phlebography are Thorotrast, 35% Diodrast and 70% Diodrast. Some objection has been raised to Thorotrast because it is radioactive and remains in the cells of the reticuloendothelial system for a long time. We have never observed any disagreeable effect from the use of the small amounts of Thorotrast necessary for phlebography. Diodrast is equally useful, however, is rapidly excreted by the kidney and does not carry the threat of radioactivity. Diodrast (35%) provides about the same density in phlebograms as Thorotrast, while 70% Diodrast gives greater contrast and is therefore preferable for visualization of the innominate vein or superior vena cava. To obtain a phlebogram of the superior vena cava or its tributaries, the patient is placed on the cassette in the supine position. Regardless of the site of the injection of the contrast medium, the venipuncture is made in the usual way with a needle of 15 to 18 gauge. The injection is made uninterruptedly and as rapidly as possible. When it is intended to visualize the innominate vein or superior vena cava, 30 cc. of the contrast medium is used, and the injection must be rapid. In all other instances, 15 cc. suffices, and speed of injection is less important. The Roentgen ray film is exposed at the moment that the injection is

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completed. The target distance is 36 inches, and the technique is the same as for a chest film with the exception that the time of exposure is doubled.

In the superior vena caval system, the only major vein which is not accessible to phlebography is the internal jugular. The procedure has relatively little use for investigation of the veins of the forearm.

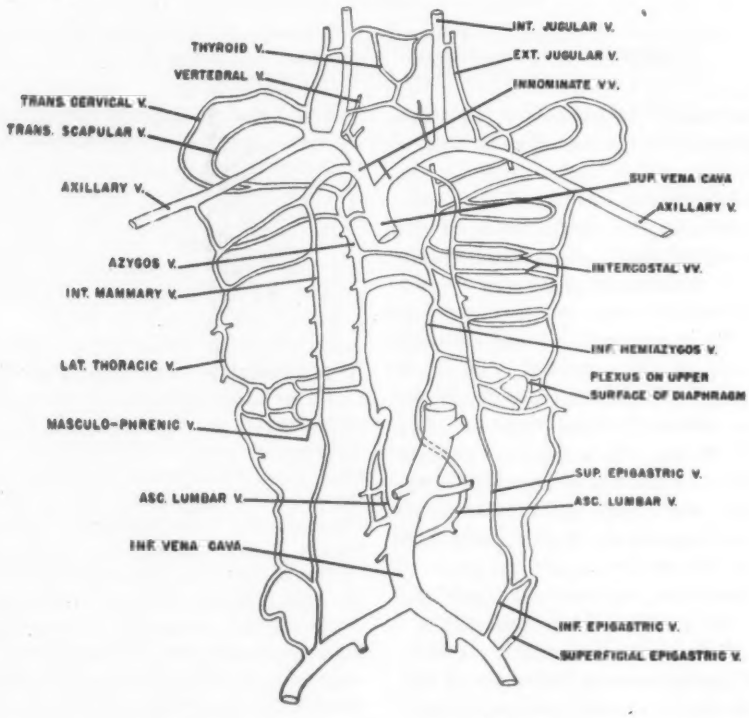



FIG. 1.—The collateral circulation in cases of superior vena caval obstruction. (After Blasinghame.)

OBSTRUCTION OF THE SUPERIOR VENA CAVA. Obstruction of the superior vena cava may be complete or incomplete. The etiology is the same in both instances. In our experience[4] the main causes have been, in order of frequency, aortic aneurysm, bronchogenic carcinoma, and mediastinal lymphoma. Less frequent causes are metastatic carcinoma of the mediastinal lymph nodes, thrombosis of the superior vena cava and mediastinitis. In a small percentage of cases, especially those without a demonstrable mediastinal mass, the cause remains obscure.

When the superior vena cava is obstructed, the location and extent of the collateral circulation depend upon the site, duration and completeness of the obstruction. With occlusion of the superior vena cava above the point of entrance of the azygos vein, this vein and its tributaries are the main collateral channels and therefore the visible collateral circulation is not extensive. A few dilated veins may be seen in the neck, shoulder regions and upper part of the chest. In contrast, when the obstruction is below the azygos vein, an extensive collateral circulation is visible on the chest and abdomen, representing the routes thereby blood from the superior vena caval system is transported to the inferior vena cava for return to

the heart (Fig. 1). The longer the duration and the more complete the degree of obstruction, the more extensive the collateral circulation will be.

The use of phlebography in the diagnosis of complete obstruction of the superior vena cava is exemplified in the following case.

**Case Reports.** CASE 1. R. B. (B50005) was a 60 year old Negro who had a malignant lymphoma of the superior mediastinum. He had dyspnea, slight facial edema, dilated veins of the chest and neck, and generalized lymphadenopathy. The venous pressure was 480 mm. of saline solution in the right arm, 450 mm. in the left arm, and rose to about 600 mm. in each arm with the "exercise test," which consists of having the patient forcefully open and clench the fist for 1 minute while the venous pressure is being measured.[9] The femoral venous pressure was 120 mm. A phlebogram made by injecting Diodrast into the right antecubital vein, clearly demonstrates the point of obstruction in the superior vena cava and the extent of the collateral circulation (Fig. 2, *A* and *B*).

Ordinarily the results of phlebography are more satisfactory in this type of case when the injection is made into the external jugular vein. When the median basilic vein is used, the superior vena cava often is not visualized, and the phlebogram may show only the collateral circulation (Fig. 3).

An example of incomplete obstruction of the superior vena cava is shown in Figure 4, *A* and *B*. These represent the phlebogram of a patient with an aneurysm of the ascending limb of the aorta.

OBSTRUCTION OF THE INNOMINATE VEIN. The etiology of innominate vein obstruction is essentially the same as for obstruction of the superior vena cava and may also be complete or incomplete. In the innominate vein thrombosis is probably more frequent than in the superior vena cava. This is explicable by the fact that thrombi in the subclavian vein may extend into the innominate but rarely go farther. The left innominate vein is more often obstructed by aneurysm of the aorta than the right, mainly because of the intimate relationship which the left innominate bears to the aortic arch.[3]

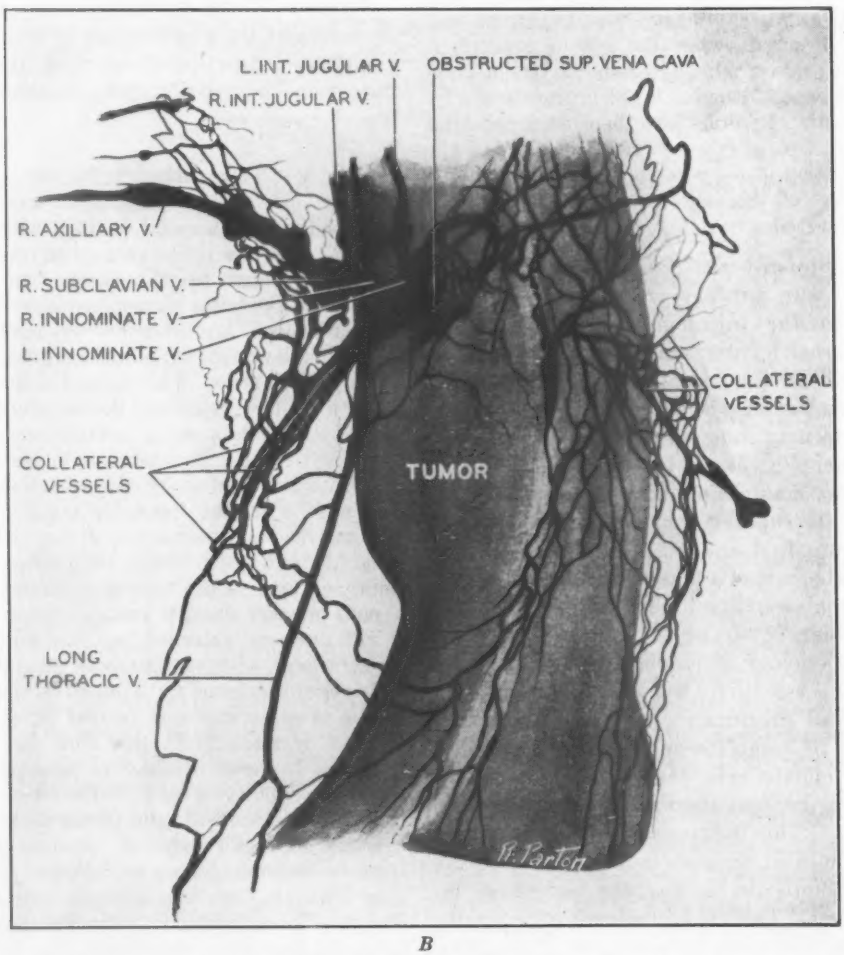
When an innominate vein is obstructed, the blood is returned to the heart from the obstructed side principally by way of the other innominate. The route follows collateral veins which traverse the midline and include all of the tributaries of the innominate, jugular and subclavian veins (Fig. 1). Judging from our experience with phlebograms, however, the subclavian and internal jugular veins are usually quite dilated, and their tributaries, especially those of the internal jugular, are a prominent part of the collateral circulation.

Figure 5, *A* and *B*, and Figure 6, *A* and *B*, represent the phlebograms in a case of complete obstruction of the right innominate vein and partial obstruction of the superior vena cava.

CASE 2. This patient (C13989) was a 64 year old colored male, who was first admitted to the hospital in 1939 with the picture of acute superior vena caval obstruction. No cause for the obstruction was found, and there was no demonstrable mediastinal tumor. A phlebogram was made by injecting Thorotrast simultaneously into the veins of both arms. This showed dilatation of both axillary veins but the remainder of the superior vena caval system was not visualized. The venous pressure in the arms was 500 mm. of saline solution with a rise to 590 mm. with the "exercise test." The femoral venous pressure was 70 mm. After 2 months of hospitalization, the patient was improved, and at the time of discharge the venous pressure was 330 mm.

This patient returned to the hospital 6 years later with symptoms of prostatism which later was found to be due to carcinoma of the prostate and was treated by transurethral resection. At this time he still appeared to have evidence of obstruction of the superior vena cava, in the form of a prominent network of veins in the neck and over the chest and abdomen. Venous pressure measurements were as follows: right arm 273 mm., left arm 232 mm., femoral 50 mm. These findings in themselves merely indicated that there was obstruction in the

*A*




*B*

FIG. 2.—Phlebogram (*A*) and drawing (*B*) of a patient with complete obstruction of the superior vena cava due to mediastinal tumor. The point of obstruction and the extensive collateral circulation are shown.

superior vena caval system, but were of little value in localizing it. There was obviously more obstruction in the right side than on the left. Precise localization was obtained by means of phlebography. Figure 5 shows the phlebogram of the right side, made by injecting 30 cc. of 70% Diodrast into the right external jugular vein. The right innominate vein is not filled beyond its first part. The subclavian and internal jugular veins and their tributaries are greatly dilated and have been filled by reflux of the contrast medium. Numerous collaterals cross the midline from the internal jugular to enter the left innominate vein. At the point where this vein enters it, the superior vena cava is somewhat narrowed. Figure 6, *A* and *B*, shows a similar study made on the left side. The left internal mammary, pericardiac and azygos veins are clearly a part of the collateral circulation.

In summary, therefore, this patient had complete obstruction of the right innominate vein and partial obstruction of the superior vena cava, presumably due to long-standing thrombosis. The studies, including those of the first period of hospitalization, would seem to indicate that the process started in the superior vena cava and extended into the right innominate vein. The adjustment made by the patient to the venous obstruction has been excellent.

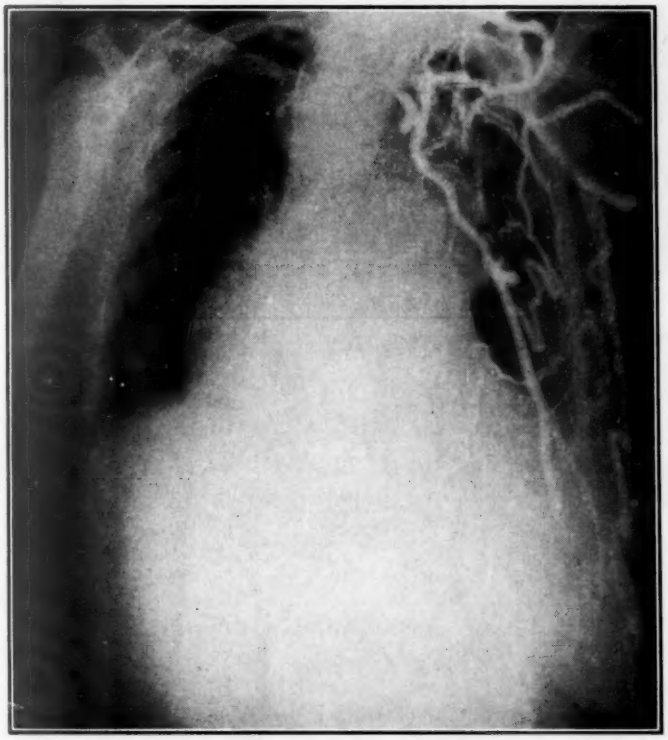
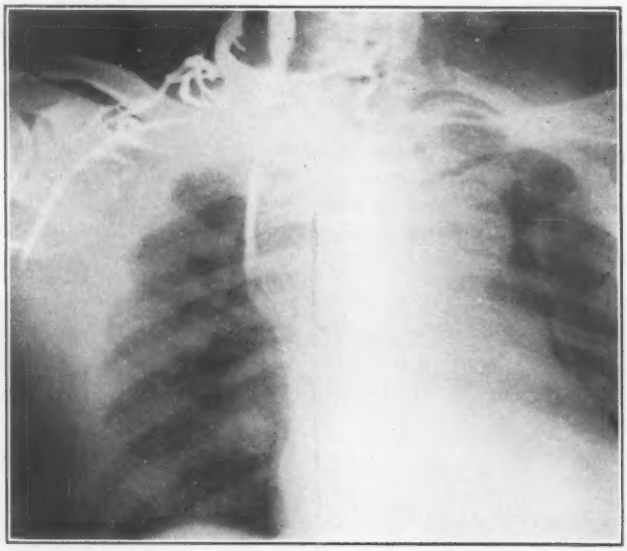


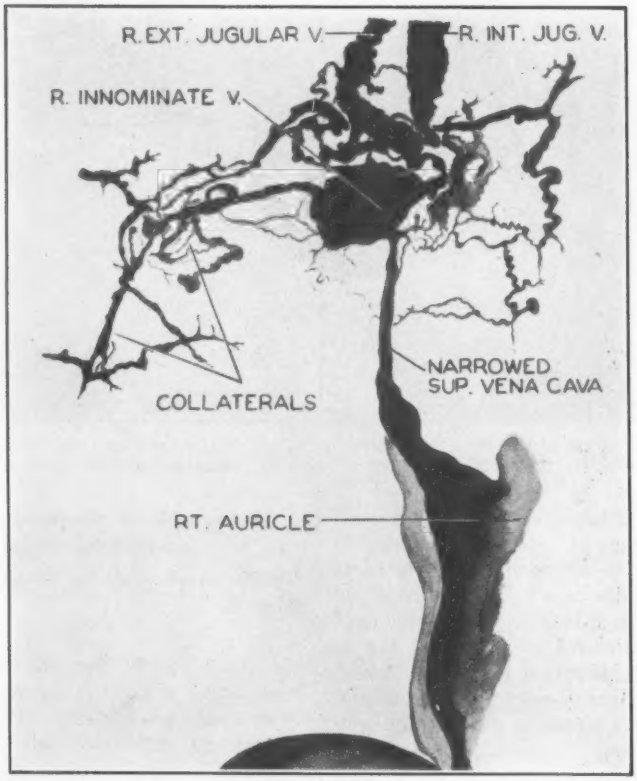
FIG. 3.—Phlebogram of a case of complete obstruction of the superior vena cava. The extensive collateral circulation is seen but the superior vena cava and its immediate tributaries are not visualized.

An example of complete obstruction of the left innominate vein is shown in Figure 7, *A* and *B*, the phlebogram of Case 3.

CASE 3. A 68 year old white male had obstruction of the left innominate vein due to metastatic carcinoma. The veins in the left pectoral region, left side of the neck and at the left shoulder were prominent. The left arm was slightly swollen. The venous pressure in this arm was 200 mm. of saline



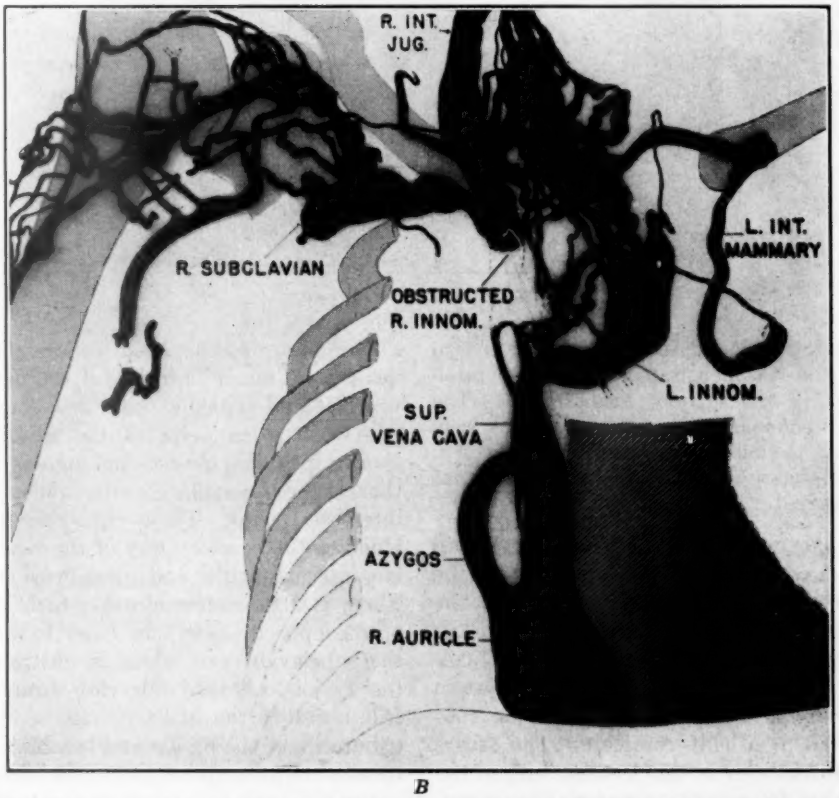
*A*




*B*

FIG. 4.—Phlebogram (*A*) and drawing (*B*) showing an incomplete obstruction of the superior vena cava due to an aneurysm of the aorta.

*A*




*B*

FIG. 5.—Phlebogram (*A*) and drawing (*B*) showing complete obstruction of the right innominate vein with filling of the left innominate and superior vena cava by way of collateral channels.

solution and rose to 280 mm. with the "exercise test." The venous pressure in the right arm was 130 mm. and did not change with the "exercise test." The phlebogram shows that the greater portions of the subclavian and innominate veins are occluded. The terminal portion of the left innominate vein is visualized at the point of junction with the right innominate and is greatly narrowed. The right internal jugular and innominate veins have been filled from the numerous collaterals which cross from the

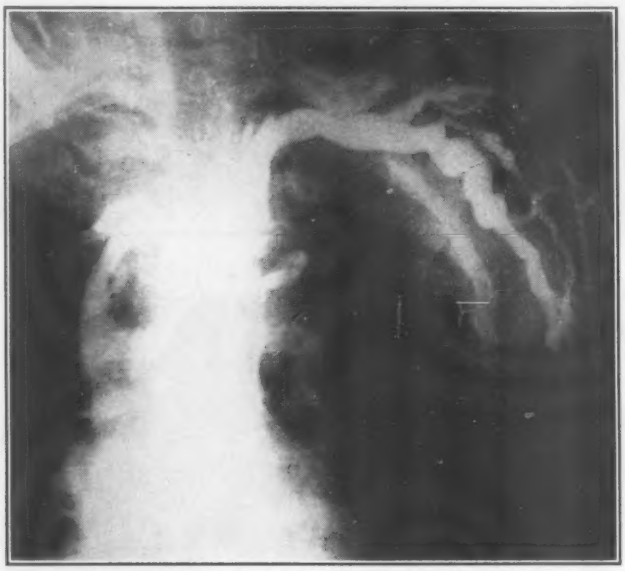


FIG. 6 *A*. (Legend on next page)

obstructed side. Autopsy examination in this case demonstrated metastatic carcinoma in the superior mediastinum. The left innominate and subclavian veins were obstructed due to invasion by the carcinoma. The primary site of the carcinoma was not discovered.

OBSTRUCTION OF THE SUBCLAVIAN AND AXILLARY VEINS. In contrast to the rarity of thrombosis as a factor in the obstruction of the innominate vein or superior vena cava, subclavian and axillary vein obstruction is commonly due to thrombosis and in the case of the subclavian, is usually complete. The causes for thrombosis in this location are, in the order of frequency, metastatic carcinoma, congestive heart failure, trauma or effort, and constriction by scar tissue.[8] Incomplete obstruction of the axillary vein is a frequent sequel of radical mastectomy and has been shown to be due to angulation of the vein at the axilla.[10]

The development of collateral circulation depends upon the site of obstruction. When the first part of the axillary vein alone is occluded, the cephalic vein is the main collateral vessel. When the entire axillary vein is obstructed, collaterals develop from minor branches of the basilic, brachial and cephalic veins to communicate with small veins of the neck and thorax, including the external jugular, long thoracic, costo-axillary, subscapular and intercostal veins. These veins return the blood to the heart by way of the subclavian, internal jugular and innominate veins. There is little communication with veins of the opposite side. In cases in which the subclavian vein alone is obstructed, the major collaterals develop from the tributaries of the axillary. In addition, tributaries of the basilic and brachial contribute. The collateral channels circumvent the obstruction and carry blood to

the jugular and innominate veins of the same side. When the axillary and subclavian veins both are obstructed, the collateral circulation is essentially the same as when the axillary vein alone is involved. The collateral network is more extensive, however, and the tributaries of the subclavian vein participate in the venous anastomosis.

An example of subclavian vein thrombosis due to trauma is shown in Figure 8, *A* and *B*, and Figure 9, *A* and *B*.

CASE 4. The patient was a young white woman who fell backward and, in attempting to break the fall, caught her weight on her outstretched right hand. By the next day, she noticed weakness and fullness of the right upper extremity. The arm was slightly swollen and cyanotic, and the veins were distended. The venous pressure in the right arm was 310 mm. and rose to 410 mm. with the "exercise test." The venous pressure in the left arm was 135 mm. At this time a phlebogram (Fig. 8, *A* and *B*) showed

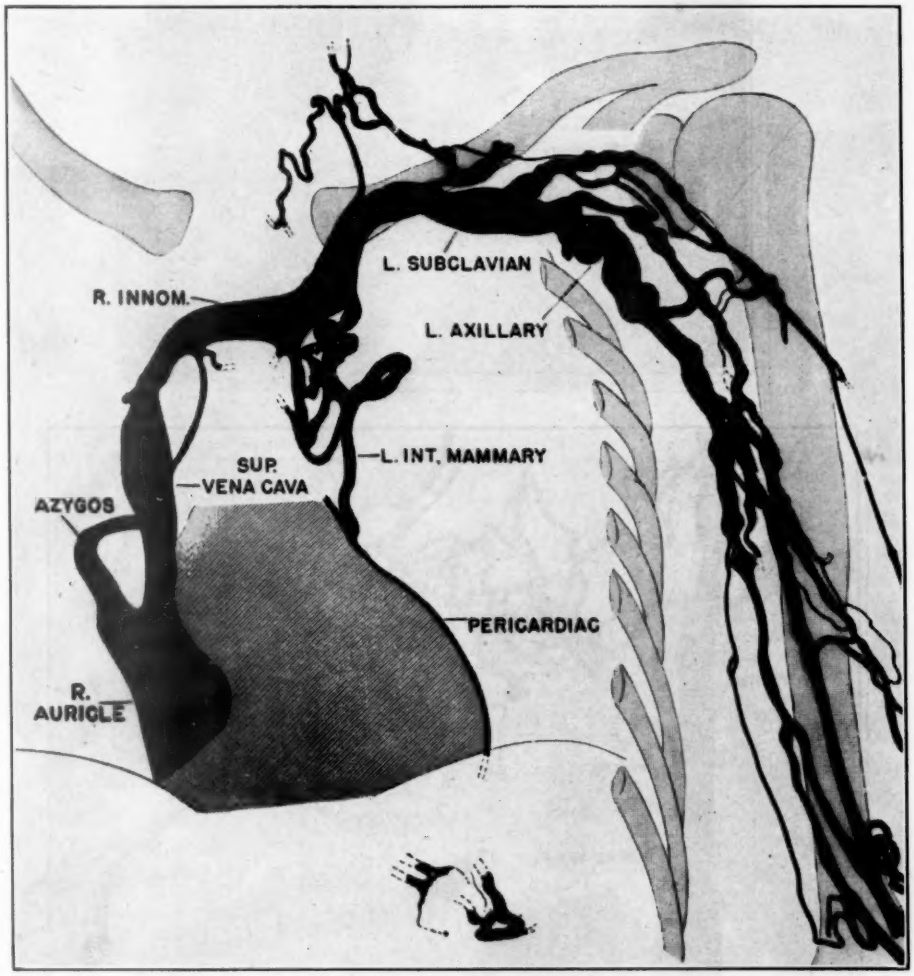
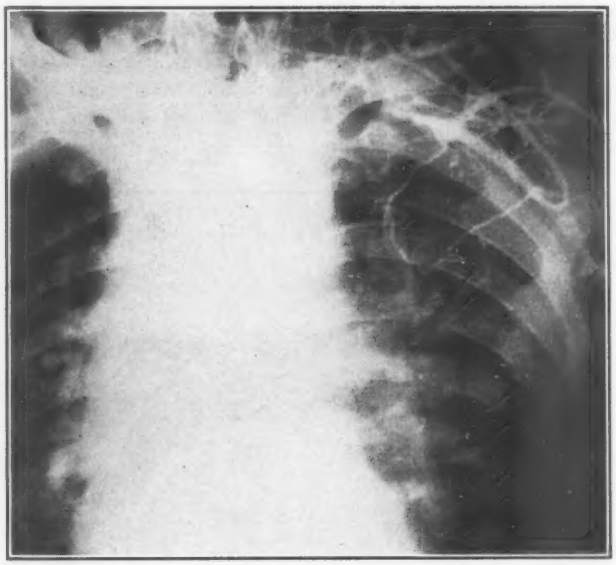
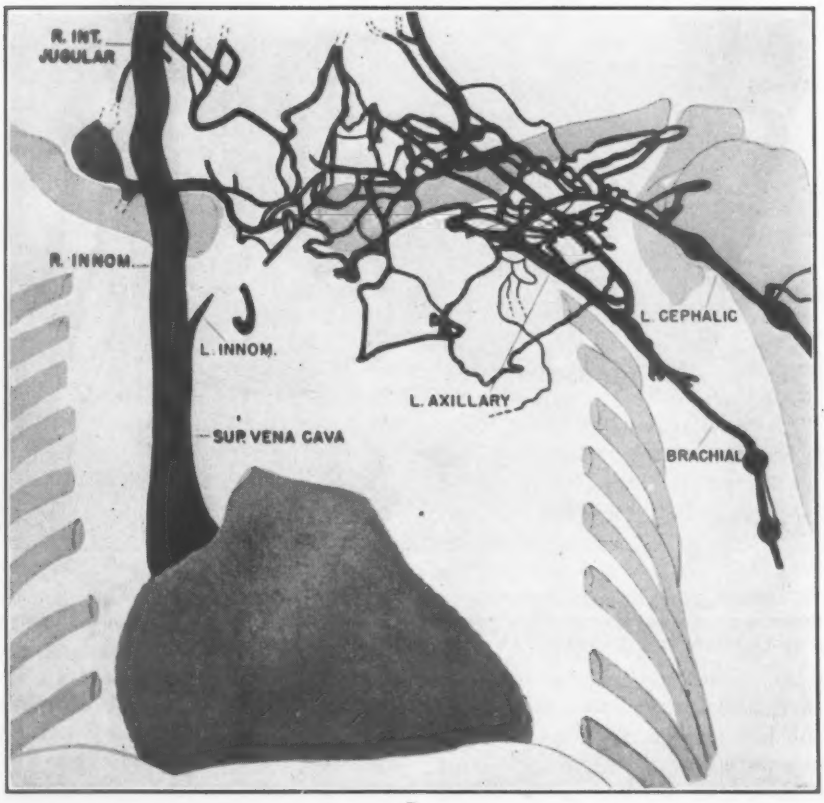



FIG. 6 *B*

FIG. 6.—Phlebogram (*A*) and drawing (*B*) visualizing the left innominate vein and its tributaries from the same case as in Figure 5. The superior vena cava is narrowed in its first part. In the drawing the vein labelled right innominate is the left innominate.



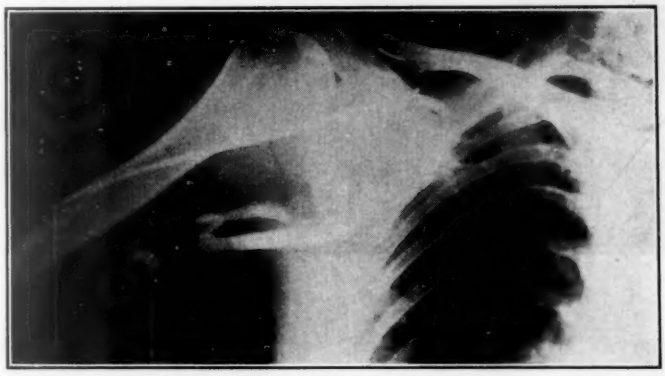
*A*



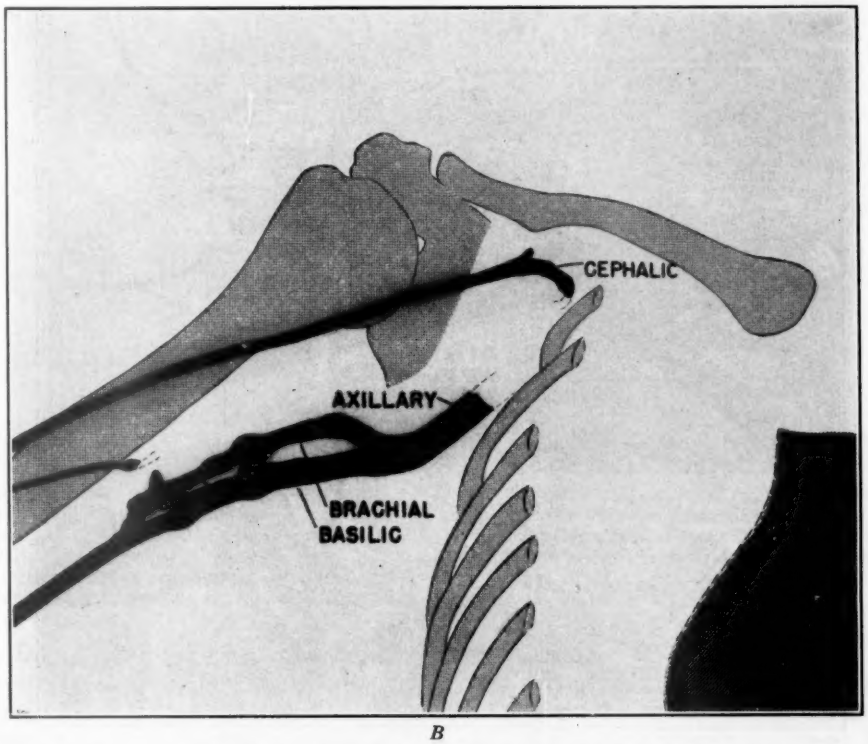

*B*

FIG. 7.—Phlebogram (*A*) and drawing (*B*) showing complete obstruction of the left innominate vein due to invasion of carcinoma.

dilatation of the brachial and axillary veins and filling of the cephalic vein which may have been retrograde or by way of collaterals in the arm. Figure 9, *A* and *B*, is from a phlebogram made 6 months later. It demonstrates a marked increase in the number of vessels with participation of branches of the axillary, brachial, basilic and cephalic veins in the collateral circulation. At this time the patient was symptom-free, an extensive network of veins was seen at the pectoral region and shoulder, and the venous pressure was within normal limits but rose about 100 mm. with the "exercise test."



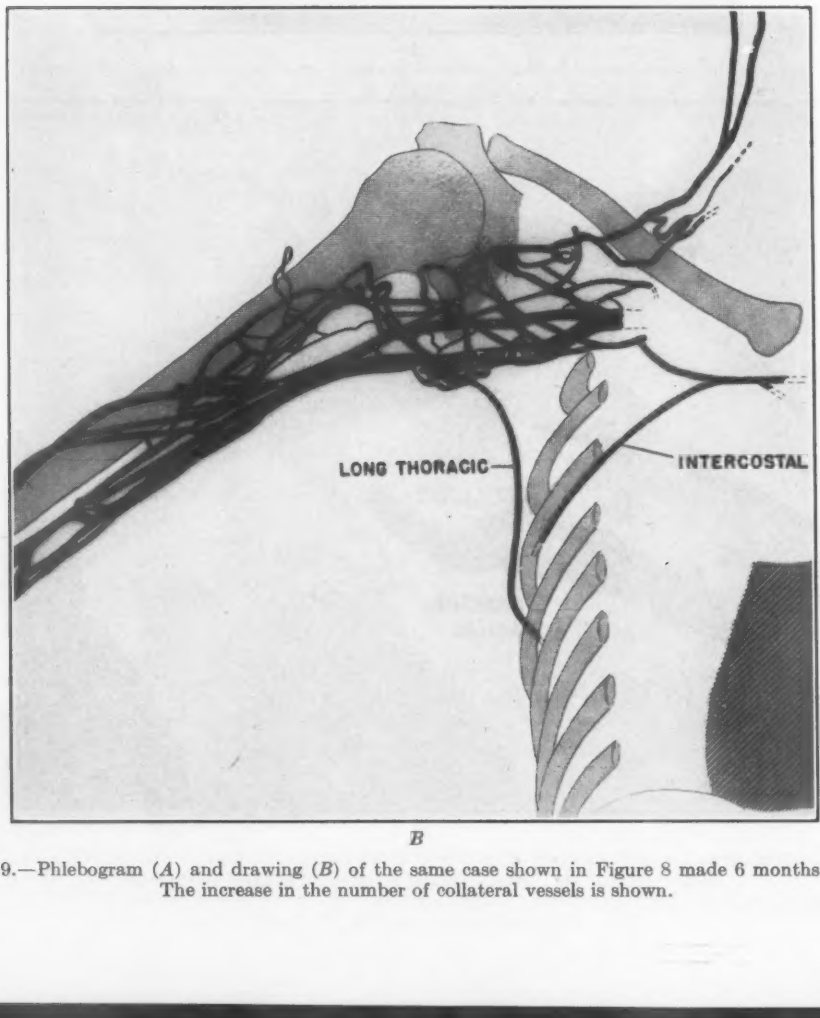
*A*




*B*

FIG. 8.—Phlebogram (*A*) and drawing (*B*) in a case of subclavian vein thrombosis due to trauma. The importance of the cephalic vein as a collateral channel is obvious.

*A*




*B*

FIG. 9.—Phlebogram (*A*) and drawing (*B*) of the same case shown in Figure 8 made 6 months later. The increase in the number of collateral vessels is shown.

Figure 10 represents a series of phlebograms showing the mechanism by which partial obstruction of the axillary vein may result following radical mastectomy. After this operation the angle at which the axillary vein enters the thorax when the patient's arm is in adduction may be so acute that the vein is obstructed. The obstruction is relieved when the arm is abducted.

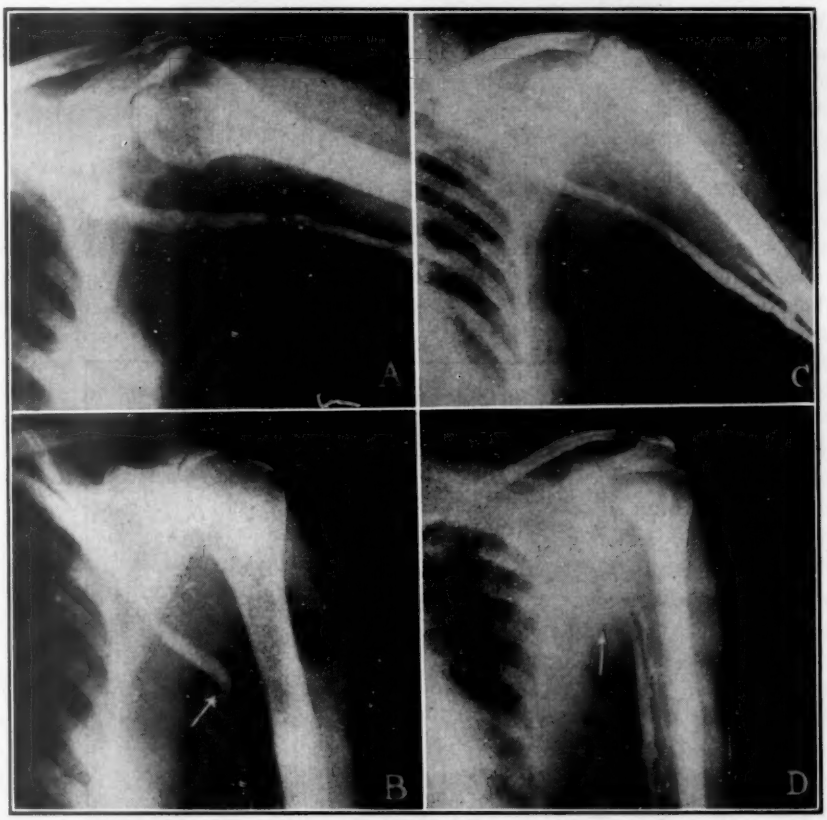
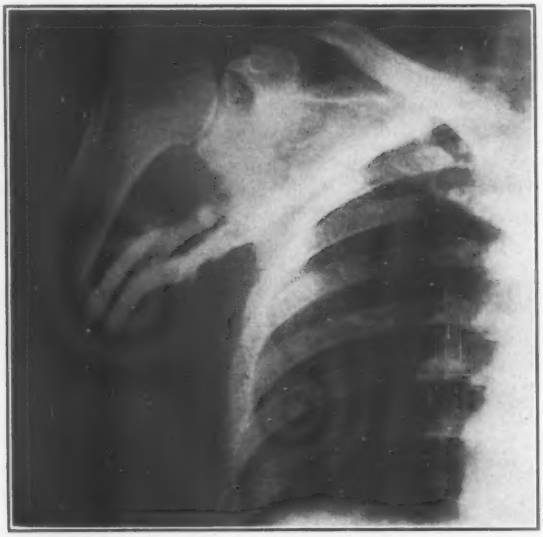



FIG. 10.—Phlebogram showing the mechanism of venous obstruction following radical mastectomy. *A*, Phlebogram showing normal axillary vein with arm abducted. *B*, Phlebogram of same patient with arm adducted. *C*, Phlebogram of axillary vein in a patient who developed edema of the arm only when the arm is dependent. Note that with the arm abducted the vein is not occluded. *D*, Phlebogram of the same patient with the arm adducted. Note complete occlusion of axillary vein (arrow) and backflow of opaque medium into tributaries.

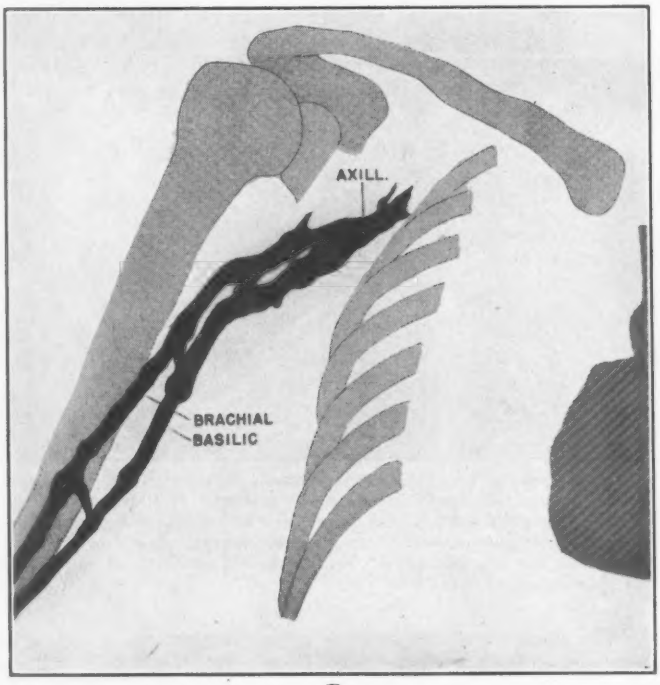
**Discussion.**—The results in the cases selected for presentation in this paper are typical of what may be expected in phlebographic study of obstructive lesions of the veins of the superior vena caval system. Phlebography provides anatomic details that otherwise could be obtained only by dissection. For example, there is no other means to differentiate clinically obstruction of both innominate veins from occlusion of the superior vena cava, or axillary vein thrombosis from obstruction of the subclavian. There is no more accurate method for study of the development and extent of the collateral venous circulation.

One of the features which adds to the attractiveness of phlebography of this type is its simplicity. No special apparatus is necessary, and the technique requires only the skill ordinarily employed in a venipuncture.

Phlebography with Diodrast is almost



*A*




*B*

FIG. 11.—Phlebogram (*A*) and drawing (*B*) in a normal patient. The film has been exposed when the contrast medium reached the subclavian vein giving the false impression of occlusion at this point.

entirely safe. Most patients experience a feeling of warmth in the face, extremities and rectum, while flushing of the face is also noted. These symptoms are mild and quite transitory, and require no treatment. Occasionally, there is brief nausea and vomiting. Less frequent toxic effects include pain along the course of the vein injected, urticaria, pruritus and a sense of constriction in the throat.

When urticaria and pruritus are especially disagreeable epinephrin gives prompt relief. Although we have never seen a serious reaction to Diodrast, there have been reported instances of severe hypersensitivity resembling anaphylactic shock.[5] It is advised that tests for hypersensitivity to the drug be performed before it is used.[1,6] This is not the place to debate whether or not Thorotrast is a safe drug for injection. We have used it many times for phlebograms and arteriograms before Diodrast was readily available, and have never seen a serious reaction, either immediate or remote, from its use for these studies. When either Diodrast or Thorotrast is accidentally injected outside a vein, local swelling and discomfort ensue. These effects are usually mild and temporary. Thorotrast remains indefinitely in the soft tissues, however, and causes a local fibroblastic reaction. We have never observed a case of phlebitis after the intravenous administration of either drug, although this complication has been recorded.[2]

The interpretation of phlebograms of the superior vena cava and its tributaries merely requires a superficial knowledge of anatomy. There is nothing like the difficulty encountered in attempts to interpret phlebograms of the deep veins of the leg in which anatomic variation is frequent and ideal visualization is difficult to obtain. An error of interpretation may occur in phlebography of the superior vena caval system when the Roentgen ray film is exposed too soon. This will give a film which shows abrupt termination of the dye-filled veins, simulating obstruction (Fig. 11, *A* and *B*). When there is doubt on this score, the phlebogram should be repeated, using a larger amount of the contrast medium, so that the exposure of the film can be made after a longer interval of time from the start of the injection.

It is desirable to have venous pressure measurements made in conjunction with a phlebographic study. When there is obstruction in the veins of the superior vena caval system, the venous pressure usually is abnormally high and rises higher with the "exercise test." It is often found that with the development of a collateral circulation, the venous pressure becomes lower and may even become normal, although the response to the "exercise test" persists. This indicates functional improvement of the venous circulation, a fact which is not apparent from the phlebographic study alone.

**Summary and Conclusions.**—Phlebography is a simple, safe, practical method for studying obstructive lesions of the superior vena caval system. This technique, in association with comparative measurements of the venous pressure, affords unequalled precision for localization of a venous obstruction and for determination of the extent and efficiency of the venous collateral circulation.

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# ALTERATIONS IN THE FORM OF THE ELECTROCARDIOGRAM IN PATIENTS WITH MENTAL DISEASE

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In 1940 Ljundberg[8] described a pattern of electrocardiographic changes occurring in a group of 90 psychotic patients. These alterations included prolongation of the P–R interval, disturbances of rhythm, notching of P waves, widening of QRS complexes, and depression of S–T segments. Meyer and Billman,[16] however, in an analysis of the electrocardiograms of 100 patients with anxiety states and depressions, failed to corroborate these findings. Our own experience during the routine study of tracings on patients suffering from mental disease revealed what seemed to be an increased incidence of deviations from the normal. Accordingly, the electrocardiograms from a group of 200 consecutive psychiatric patients were selected for analysis, and compared with the tracings of 200 individuals without mental disease, who were free of cardiac abnormalities.

*Material and Method of Study.* The limb leads, plus lead CF4, were taken on all of the psychiatric patients and normal subjects. In most of the patients lead CF5 was also obtained. All recordings were made in the supine posture. All of the patients with mental disease and all of the subjects in the non-psychiatric group had had a physical examination and were free of objective evidence of heart disease. The observations were made in a county hospital and in an army general hospital. The 200 psychiatric patients were being routinely studied to determine their physical fitness to undergo electric shock therapy; 194 were suffering from psychosis, including schizophrenia, manic-depressive psychosis, and dementia præcox; 4 were diagnosed as psychoneurosis with reactive depression, and 2 as having the constitutional psychopathic state. In the mentally ill group there were 182 men and 18 women. The age incidence of this group ranged from 18 to 64 years, with the majority falling in the 3rd and 4th decades. The age incidence of the non-psychiatric group varied from 17 to 60 years, with the greatest number of subjects also occurring in the 3rd and 4th decades. There were 158 men and 42 women in the control group.

Results. The results are summarized in the table given on page 24.

**Discussion.** Forty-three psychiatric patients (21.5%) revealed 1 or more of the following aberrations of the electrocardiogram: (1) a P–R interval above 0.20 second; (2) a decrease in the amplitude of R4 or R5 to less than 1.5 mm.; (3) T waves of low amplitude (less than 0.5 mm.), or diphasic T waves, in lead I; (4) inverted or diphasic T4 or T5; (5) the Wolff-Parkinson-White syndrome; (6) paroxysmal auricular tachycardia; (7) auricular flutter. In contrast, only 6 (3%) of the non-psychiatric patients showed 1 or more of these findings. Thus, the occurrence of these alterations was found over 7 times more frequently in the psychiatric group than in the non-psychiatric group.

As seen in Table 1, there was increased incidence (3%) of prolongation of the P–R interval in the psychiatric patients, as compared with the normal subjects. This 3% incidence is also almost double that found in a group of 1000 healthy aviators,[4] where only 1.6% of the subjects revealed such prolongations.

The less frequent incidence of short P–R intervals (less than 0.14 second) in the psychiatric group is noteworthy; furthermore, this frequency of such short P–R intervals in the patients with mental disease is much less than in the previously cited series of healthy aviators, in whom Graybiel *et al.*[4] found an incidence of 17.2% of P–R intervals below 0.14 second. The combination of an increased number of long P–R intervals, and a decreased number of short P–R intervals in the psychiatric patients suggests a vagotonic state. The influence of vagal overactivity (produced by mecholyl and prostigmin) in causing prolongation of auriculoventricular conduction time is well recognized.[2] Moreover, Logue, Hanson and Knight[11] found that in a group of 150 patients with neurocirculatory asthenia, 7 (4.6%) revealed a prolongation of the P–R interval above normal limits.

Table 1.—Electrocardiographic Findings in 200 Psychiatric Patients and and 200 Normal Subjects

| | No. cases in non-psychiatric group | No. cases in psychiatric group |
|---|---|---|
| P–R less than 0.14 second* | 20 | 11 |
| P–R greater than 0.20 second | 1 | 6† |
| R4 or 5 less than 1.5 mm. | 4 | 10 |
| T1 less than 0.5 mm.* | 0 | 11 |
| T2 less than 0.5 mm.* | 2 | 9 |
| T4 or T5 inverted or diphasic* | 1 | 16 |
| Wolff-Parkinson-White syndrome | 0 | 4 |
| Auricular paroxysmal tachycardia | 0 | 1 |
| Paroxysmal auricular flutter | 0 | 1 |

* Exclusive of cases with Wolff-Parkinson-White syndrome.

† The P–R intervals in this group were as follows: 0.26 second (1 patient), 0.24 second (1 patient), 0.22 second (3 patients) and 0.21 second (1 patient).

The frequency of T-wave changes in the psychiatric group as compared with the subjects with normal hearts is of considerable interest. The literature reveals ample evidence that autonomic imbalance and emotional disturbances may produce abnormalities of the T waves. It has been shown that various types of adrenergic stimuli may produce lowered voltage of the T waves. The injection of adrenalin into normal subjects has been shown to produce decreased amplitude of the T waves.[6,7] Wendkos,[19] and Wendkos and Logue[20] have shown that increased sympathetic activity may produce inversion of the T waves in precordial leads and in in leads II and III, as well as lowered voltage in lead I. Recently Robb[17] has shown that direct electrical stimulation of the cardiac sympathetic nerves may produce lowering and inversion of the T waves in dogs. That cholinergic stimuli may also produce abnormalities of T waves is suggested by the finding that inversion of T waves in precordial leads may be produced by the administration of a sympatholytic drug (ergotamine) to emotionally unstable persons without organic heart disease.[19]

Mainzer and Krause[13] have shown that fear may produce inversion of the T waves in patients about to undergo surgical operations. Loftus, Gold and Diethelm[9] have reported the case of a psychiatric patient in whom periods of intense anxiety were accompanied by marked lowering of the T waves in leads I and II. Several investigators[5,11,15,19,20] have shown that emotional instability and neurocirculatory asthenia may produce T-wave changes in patients free of organic heart disease. Thus, Logue *et al.*[11] found low voltage of the T waves in lead I, in 22 of a group of 150 patients with neurocirculatory asthenia, who were free of organic heart disease. The T waves in this latter group were also found to show aberrations in lead 2 in 21 cases.

The occurrence of a short P–R, wide QRS complex in 4 of the mental patients,

and the absence of such findings in any of the normal group would seem to be more than coincidence. The 2% incidence of this abnormality is 10 times as great as its frequency in the series of 1000 normal subjects reported by Graybiel *et al.*,[4] who found an incidence of only 0.2% in their series. The patient with auricular flutter is of special interest. He was found to have 2:1 block, with an auricular rate of 360 and a ventricular rate of 180. This patient was a 60 year old white male, who was admitted in a state of severe depression with suicidal tendencies. Careful physical examination failed to reveal evidence of heart disease, and the blood pressure was found to be normal. The abnormal cardiac mechanism subsided without treatment, and 2 subsequent electrocardiograms taken 3 and 12 days after the episode, were within normal limits.

The exact mechanism of production of these alterations of the electrocardiogram is obscure. However, in view of the similarity of these changes to those produced by transient emotional disturbances, as well as those caused by artificial stimulation of the sympathetic and parasympathetic systems, cited above, it would seem that both emotional instability and abnormal autonomic activity were operative in the present series of psychiatric patients. These previous observations of other investigators seem to leave little doubt that nervous influences play an important rôle in determining the form of the electrocardiogram. Severe emotional disturbances were unquestionably existent in the present group of psychiatric patients. The precise portion of the autonomic nervous system which may have been hyperactive at any moment in these patients is difficult to determine. However, the nature of the aberrations noted in the present study would seem to indicate the possibility that both adrenergic and cholinergic stimuli were operative in this group of mentally diseased patients.

The probable emotional basis of the changes observed in the psychiatric group renders it possible that in some normal individuals, similar changes might be produced by the stress of fright occurring during electrocardiographic examinations. These findings tend to expand further the broadening concepts of "normalcy" necessary for a proper appraisal of electrocardiographic changes seen in persons without heart disease. Since only 1 tracing was taken in most of the present series of patients, it could not be determined if the aberrations were permanent or transient. Their apparently benign nature, however, would indicate that caution is needed in interpreting such findings as abnormal when they are encountered in patients suffering from mental disease.

**Summary.** In a series of 200 patients with mental disease a high incidence of electrocardiographic aberrations was noted as compared with 200 normal subjects. Definite changes were noted in 21.5% of the psychiatric patients, as compared with a frequency of only 3% of such changes in the normal subjects. The similarity of many of these changes to those produced by emotional stimuli, and by artificial means of stimulation of the autonomic nervous system, is discussed. The need for caution in interpreting such findings as abnormal, when they are seen in mentally ill patients, or in normal persons who are temporarily emotionally disturbed, is pointed out.

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# CICATRIZING ENTEROCOLITIS IN A NEWBORN INFANT

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Since the original description of terminal ileitis by Crohn, Ginzberg and Oppenheimer[6] in 1932, other authors have shown that this pathologic process is not necessarily confined to the terminal ileum. Harris, Bell and Brunn[10] reported the occurrence of a similar enteritis in the jejunum, and Brown, Bargen and Weber[3] as well as Crohn and Rosenak[5] later noted its appearance in the colon.

Regional enteritis, as it is now commonly designated, has been reported in Meckel's diverticulum,[4,11] and the similarity between regional enteritis and fibroplastic appendicitis has been shown by Ravdin and Rhoads.[12] Additional reports[1,4,8] indicate that the same pathologic process may involve any segment of the bowel from the duodenum[9] to the colon. Erskine[7] reported a case of acute terminal ileitis with acute appendicitis, mesenteric adenitis, salpingitis, and peritonitis in an 18 day old infant.

There appears to be no published report of the chronic form of this entity in the newborn, nor any instance in which the entire large and small bowel were involved in the pathologic process. For these reasons, it seems of interest to record the following case.

*Case History.* B. D. After an uneventful and short labor, a full-term, colored, male baby was spontaneously delivered on Dec. 8, 1945. By the 2nd day of life he had vomited repeatedly, developed abdominal distention and had passed only 1 small meconium stool. The vomitus was an odorless yellow-green liquid containing mucus. A small tube was inserted into the rectum without difficulty, and much flatus and a plug of meconium were expelled. The distention recurred but was promptly relieved by a small colonic irrigation. A flat plate of the abdomen revealed gas in both the small and large bowel but was not abnormal. On December 15, the child was discharged having returned almost to its birth weight. Distention recurred a week after discharge but was again effectively treated with the passage of a rectal tube.

On December 28, the child, then 3 weeks of age, was readmitted because of vomiting, diarrhea and abdominal distention of 2 days duration. On admission he was thin, moderately dehydrated, and his abdomen was distended. Loops of bowel could be seen and palpated through the abdominal wall, but no masses or organs could be felt. Peristalsis was obstructive, and the character of the vomitus was identical with that of the stool. The remainder of the physical examination was essentially negative. A flat plate of the abdomen (Fig. 1) was reported as possible intestinal obstruction at the ileocecal valve. Twelve hours were spent in the administration of parenteral fluids, chemotherapy and preparation of the patient for laparotomy.

At *operation*, there was great distention of the small bowel proximal to the ileocecal valve. The cecum was located in its normal position in the right lower quadrant. The ileocecal valve appeared abnormal externally as though intussusception of the ileum into the cecum had begun. The terminal small bowel and the ascending colon were the site of an inflammatory process. The bowel wall was thick and the vessels engorged. As the bowel was being carefully lifted up, a small hole was accidentally torn in the friable cecum. Through this hole the ileocecal valve was explored. There was no actual intussusception. It was possible to insert a grooved director through the ileocecal valve into the terminal ileum. At this point the infant went into peripheral collapse, despite an

intravenous infusion of blood; and therefore every effort was made to get him off the operating table as soon as possible. A No. 10 rubber catheter was passed through the opening in the cecum into the terminal ileum and sutured in place to serve as a means of decompression. The abdominal contents were replaced in the peritoneal cavity only with great difficulty.

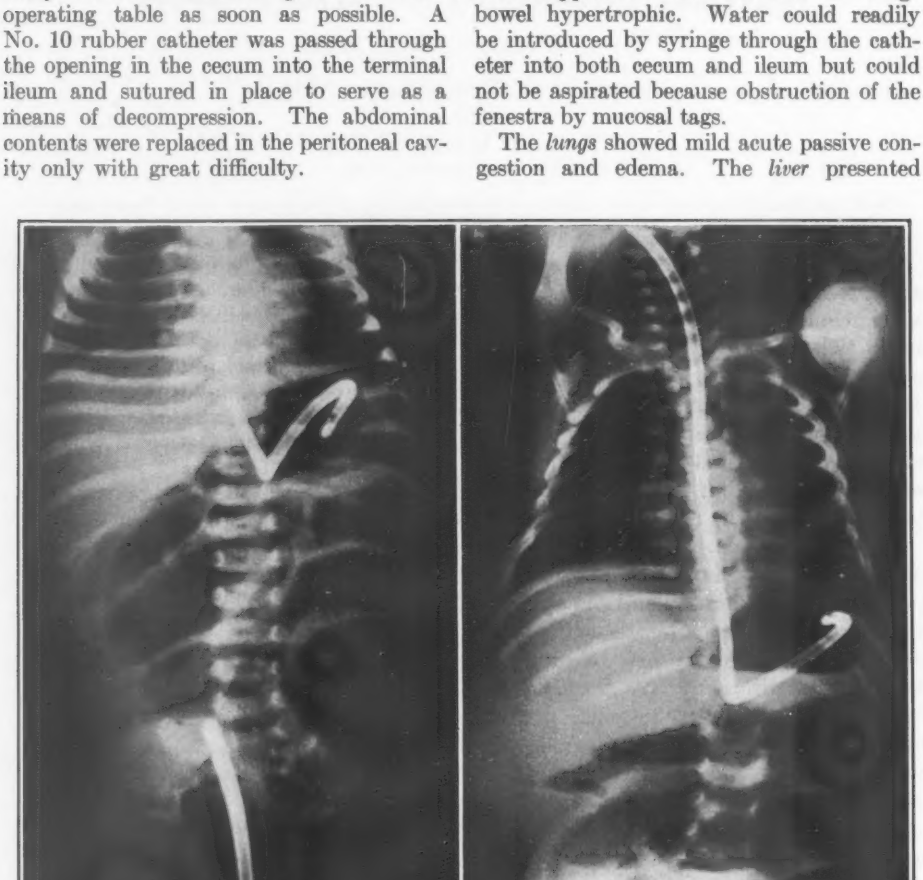

FIG. 1.—Flat plate of the abdomen taken several hours after admission. Supine film on the left, erect film on the right.

The postoperative course was progressively down hill despite chemotherapy, the parenteral administration of fluids, plasma and blood and other supportive therapy. The abdominal distention was relieved but little by the ileostomy, and peristaltic activity was never restored. On the 3rd postoperative day the infant died.

AUTOPSY. (Univ. of Penna., 1946–1, 7 hours postmortem.) The body exhibited malnutrition, dehydration, scleral icterus and abdominal distention. There was a generalized fibrinous peritonitis and a droplet of pus was uncovered about the entrance of the catheter into the cecum. *In situ* the small bowel appeared distended and the large bowel hypertrophic. Water could readily be introduced by syringe through the catheter into both cecum and ileum but could not be aspirated because obstruction of the fenestra by mucosal tags.

The *lungs* showed mild acute passive congestion and edema. The *liver* presented fatty dystrophy and some of its canaliculi were filled with bile pigment casts. The *kidneys* showed a few scattered convoluted tubules in which the epithelium was replaced by calcium deposits.

The lesions of interest were in the intestinal tract. The *esophagus* and *stomach* were normal. The serosa of the intestines was covered in places with fibrinous exudate, and exhibited dark green discolored patches. The entire small bowel was dilated. The wall of the proximal *small bowel* was thickened but friable throughout. The thickening increased from the duodenum distally

and was maximal at the ileocecal valve, appendix, cecum and ascending colon but then lessened gradually toward the anus. In the colon the thickening involved the submucosa, muscularis, and the tissue external to the muscular coat (Fig. 2). The mucosa of the distal two-thirds of the ileum appeared gray-brown and friable; it peeled off easily and was absent in thin transverse patches. The mucosa of the *colon* from the ileocecal valve to the anus had a thickened cobblestone appearance. In the sigmoid there was a small, round, punched-out ulcer about 3 mm. in diameter with a ragged base. There was a no point of frank obstruction.

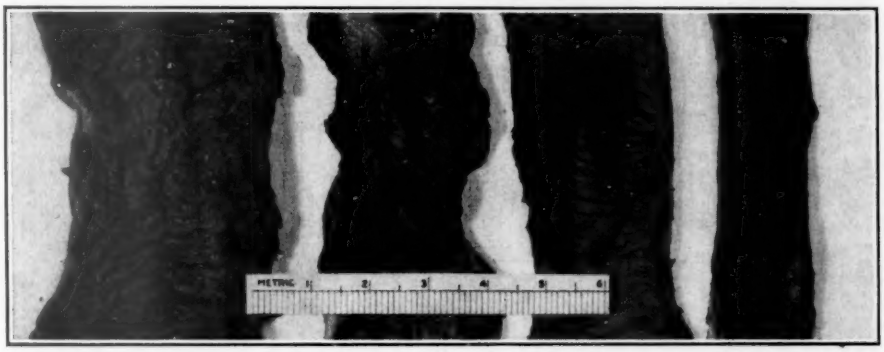

FIG. 2.—Bowel of 3 weeks old B. D. compared with normal bowel of 6 weeks old infant. 1, Colon of B. D.; 2, normal colon; 3, ileum of B. D.; 4, normal ileum.

On section, the wall was thickened not only in its submucosa but also in its musculature, including the muscularis mucosæ. This was evident by comparison of similar sections of small and large bowel of a normal 6 weeks old infant (Fig. 3). The thickening, however, was due more to the inflammatory changes in the submucosa and subserosa than to hypertrophy of the muscularis.

*Microscopic examination* of the proximal ileum showed some autolysis but, nevertheless, it was obvious that the wall was thickened. The musculature was hypertrophic; the submucosa and subserosa were thickened by fibrosis, hypermia, edema, and an exudate of cells which were difficult to recognize because of the autolysis. The distal ileum showed similar changes, but they were more marked. The exudate was composed of mononuclear leukocytes, small and large; they were characterized by round, dense nuclei and varying amounts of cytoplasm which was sometimes basophilic. In some cells the nucleus was eccentric. Lymphatics often contained exudate. In addition, there was necrosis of the mucosa and part of the submucosa, with a mild superimposed polymorphonuclear response.

The colon exhibited a most pronounced picture of chronic inflammation, fibrosis and hypertrophy of the muscular coats (Fig. 4). The mucosa was thrown into high thick folds and fibrosis was marked in the submucosa and the tissue external to the muscularis. The histologic appearance varied considerably from place to place. The mononuclear exudate was more marked in some places than in others while fibrosis was prominent elsewhere. Often fibroblasts and new vessel formation were apparent. There were no giant cells. There were occasional eosinophils and often macrophages with finely vacuolated cytoplasm. Occasionally there was fibrinoid degeneration of collagen. Some arteries had thickened dense adventitia. Occasional small vessels contained platelet thrombi enmeshing red cells and leukocytes. The appendix showed similar changes.

A section of the sigmoid ulcer showed a defect which involved the mucosa, submucosa, and part of the muscularis and which undermined the mucosal edges. The base was necrotic and the submucosa along the edges was greatly thickened by the same changes described above, but eosinophilic leukocytes occurred frequently. In the rest of the section the changes were much less evident than those higher in the colon.

The mesentery was greatly thickened, and the lymph nodes were enlarged, soft, discrete

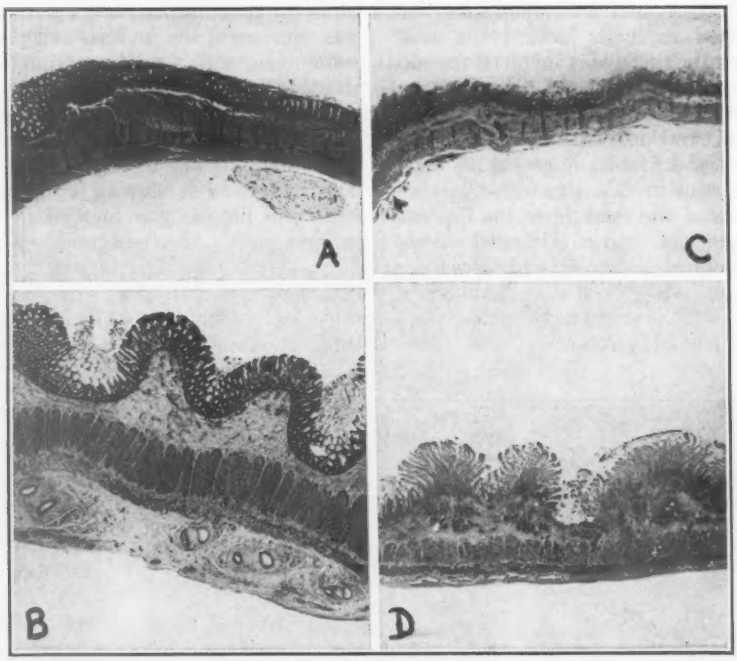


FIG. 3.—Photomicrographs of sections of bowel; B. D. compared with normal. *A*, Normal colon; *B*, enlarged colon of B. D.; *C*, normal ileum; *D*, enlarged ileum of B. D. × 10.

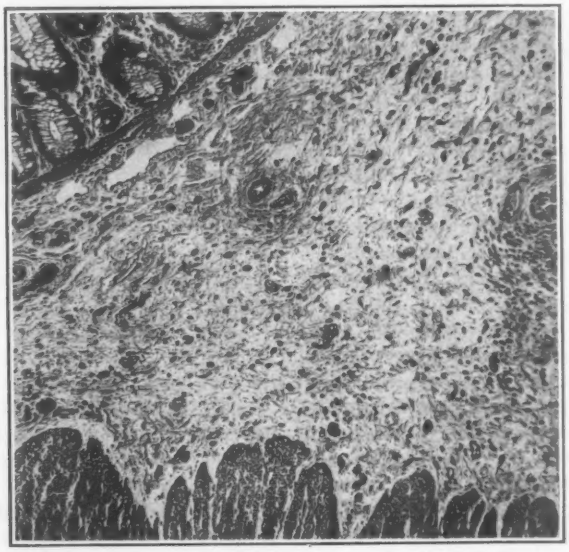

FIG. 4.—Case B. D. Photomicrograph of submucosa of colon. Note marked fibrosis and mononuclear exudate. × 73.

and pale gray in color. The mesenteric serosa showed an acute fibrinous inflammation, part of the generalized peritonitis. The chronic inflammation seen in the wall of the bowel was also present in the mesentery (Fig. 5) but, in addition, there were foci of polymorphonuclear cells scattered about. The arteries showed marked dense advential thickening (as if it were part of the general fibrosis), and the elastic laminæ were thrown into deep folds. The lumens appeared relatively small. Similar but milder changes were seen in the connective tissue about the pancreas.

**Comment.** As the infant died when less than a month old, it would seem from the chronic nature of the process (chronic inflammation, fibrosis and hypertrophy of the bowel) that it had begun *in utero.* The fact that symptoms and signs were present from birth may well support this assumption.

Physical examination and barium study of the mother's gastro-intestinal tract revealed no demonstrable lesion other than a cystocele. She had been in good health throughout her entire pregnancy and was Rh positive.

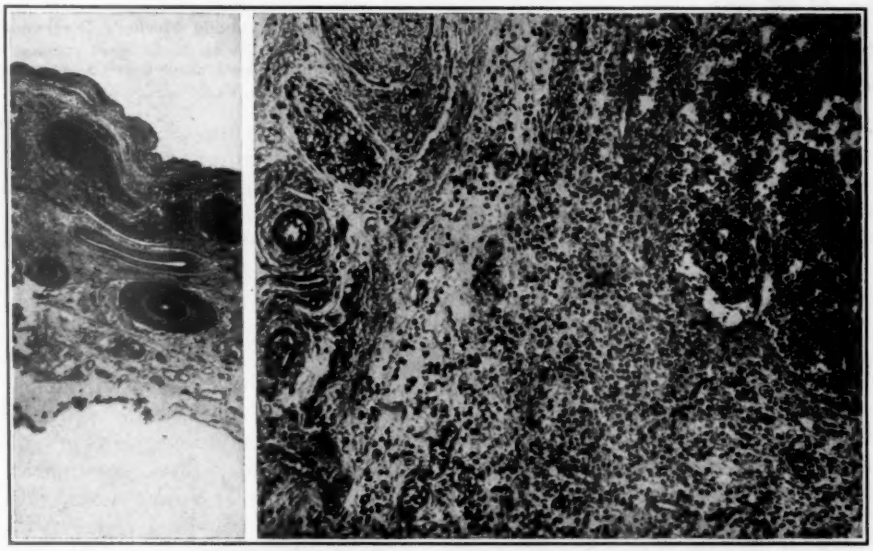

FIG. 5.—Case B. D. Thickened mesentery. Left: illustrates thickened narrowed mesenteric vessels. × 8. Right: shows fibrosis and mononuclear exudate, with portion of lymph node at extreme right. × 73.

The *lymph nodes* were depleted of lymphocytes. The sinusoids contained numerous small and large mononuclears and sometimes neutrophils, although the nuclei tended to be pyknotic so that the cells were difficult to classify. The macrophages in both the nodes and the mesenteric connective tissue often had a fine pale vacuolization in their cytoplasm.

Loeffler stains revealed no bacteria in bowel, mesentery, or mesenteric nodes. Cultures were not taken. Fat stains showed no fat in the macrophages of bowel or mesentery.

**Summary.** A unique case of chronic enterocolitis involving the entire small and large bowel in a newborn is reported. It seems likely that this lesion had its origin in prenatal life.

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# THE NEUROMUSCULAR SYSTEM IN RHEUMATOID ARTHRITIS

## ELECTROMYOGRAPHIC AND HISTOLOGIC OBSERVATIONS*†

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Muscle weakness, usually associated with atrophy, constitutes one of the most disabling features of rheumatoid arthritis. If the muscle atrophy becomes established, it undoubtedly contributes to joint deformity and presents a major hindrance to the regaining of the normal joint function. In addition, early in the disease, motor weakness, often accompanied by numbness and paresthesias, may strongly suggest the diagnosis of a primary neurologic disorder. The problem of muscular atrophy in arthritis has attracted the attention of numerous clinical observers and has led to animal experimentation in an attempt to elucidate its origin. Since rheumatoid arthritis cannot be reproduced in animals, the present investigation is entirely upon the human subject and utilizes both electromyographic tracings and histologic studies of the central nervous system, the peripheral nerves and the voluntary muscles.

**Electromyographic Observations.** The observations which were made with the aid of electromyographic tracings were divided into several parts. The first comprised the recording of voluntary contractions, which were compared with those obtained from normal individuals. In the second part, the object was to ascertain whether or not involuntary activity was present, such as is seen, for example, in progressive muscular atrophy in the form of fasciculations.‡ Finally since the increased reflexes and even clonus[34,38] often found in rheumatoid arthritis suggest spasticity, we looked for the 2 outstanding electromyographic characteristics of this state, which have recently been pointed out by Hoefer and Putnam.[29] These are synchronization in pattern and frequencies of motor unit records when 2 or more coaxial electrodes are inserted into a muscle during a gentle voluntary contraction and a spread of tendon reflexes to muscles served by reflex arcs at other levels or even on the opposite side of the body. We may anticipate the description of our results by stating here

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‡ Throughout this paper, the commonly understood distinction between fasciculations and fibrillations will be adhered to. The former, which are visible through the skin, are considered to be contractions of groups of muscle fibers making up single motor units. Fibrillations, on the other hand, which can be seen only through mucous membrane or on the surface of an exposed muscle, represent contractions of single muscle fibers and arise consequent to denervation. Another possibility suggested by recent observations[16,27] should be mentioned, that synchronized fibrillations may result in "fasciculations."

that tracings from voluntary and reflex muscle contractions in patients with rheumatoid arthritis showed no apparent deviation from the normal and gave no hint of spasticity. We did find involuntary muscular activity, however, which we attempted to define by comparison with that recorded in recognized neuromuscular disorders and to delimit its point of origin by procaine block of the common peroneal nerves.

**Material and Methods.** The largest group of patients tested comprised those with well-marked rheumatoid arthritis, 34 in number. These were all being treated on the hospital wards and were therefore, with 1 exception, of moderate or marked severity. There were 16 males and 18 females, with ages ranging from 12 to 58, with a mean of 35.6. The duration of the disease varied from 6 months to 13 years, with a mean of 5.2 years. Six of the patients, all males, had involvement of the spine in addition to peripheral joints. No form of selection was used and the patients represented a cross-section of the disease as seen in hospital practice. As a corollary to the study of the patients with rheumatoid arthritis, an additional group of patients with articular, muscular, or neurologic disease was tested for involuntary muscular activity. These comprised 3 patients with acute gonorrheal arthritis, 1 patient with acute specific infectious arthritis of unknown etiology, 2 patients with Charcot joints secondary to tabes dorsalis, 1 patient with joint disability following fixation, 1 patient with dermatomyositis and 2 patients with progressive muscular atrophy. As a final check, the muscles of 10 normal controls were tested for evidence of spontaneous activity.

The muscles chosen for examination were those in relationship to involved joints and included in the upper extremity, the triceps, biceps and the flexor and extensor muscles of the forearm. In the leg, the quadriceps, hamstring group, anterior tibial and gastrocnemius were most commonly tested. The results obtained from each were similar and did not vary in respect to the muscle chosen. In the normal controls, we searched for involuntary activity in all of the arm and leg muscles listed above.

Both surface and needle electrodes were used to obtain the action potentials from the muscles. The former were flat solder disks, 6 to 10 mm. in diameter and attached to No. 32 enamelled copper wire. The skin above the muscles to be studied was cleansed with acetone, Sanborn electrocardiographic paste was applied and the electrodes were kept in place with adhesive tape. Two such electrodes constituted a bi-polar lead and were placed 3 to 4 cm. apart along the axis of the muscle. The usual resistance in such a placement was 5000 to 10,000 ohms. Contraction of the muscle under the skin did not displace the electrodes and other sources of artefact such as motion in the electrode wires were carefully avoided. The needle electrodes were usually made of an insulated copper wire held in place within a hypodermic needle. The exposed end of the copper wire formed 1 electrode and the needle itself the other. Another method was to insert into the muscle a needle large enough to permit the passage of 2 30-gauge wires free from insulation only at the tips, which were kept slightly separated. With the wires in place within the muscle, the needle was withdrawn, leaving a bi-polar electrode consisting of 2 wires rather than a wire within a needle. The gain on the amplifiers was set so that in the relaxed *normal* muscle no deflection of the pens occurred. This represented a 1 cm. deflection for 100 microvolts of input during inactivity and for 300 microvolts during voluntary contractions.

Amplification and recording of the muscle action currents were obtained by 2 types of ink-writing oscillographs, with both giving similar results. One was a Grass 3 channel instrument with paper speeds varying from 1.5 to 6 cm. per second. With the second, designed and built by Loomis,[37] recordings could be made simultaneously in 6 channels at a paper speed of 3 cm. a second. The characteristics of both of these amplifiers are identical in that they have the first 2 or 3 stages entirely dependent on battery sources of power before feeding the power amplifiers run from commercial 60 cycle current. Both are linear up to several thousand cycles and have time constants of $\frac{3}{4}$ second. Both are condenser coupled with push-pull circuits and especially suited for the operation of the moving coil type of ink-writing oscillographs used in recording alternation potentials from 1 to 70 cycles.

The limitations of this method of recording for electromyography have been a source

of controversy, as it fails to record the wave form above 70 cycles and registers only a fraction of the potential of fibrillary spikes which last 1 to 3 milli-seconds. On the other hand, the advantage of being able to record continuously from several muscles with immediate availability of the record can only be obtained with ink-writing oscillographs. Records of film exposed to the cathode ray, which records all of the fast frequencies up to many thousand cycles, give a picture free of the disadvantages described above; but such records are not visible until the film has been developed and multiple recording is both difficult and expensive. Changes in the electromyogram that occur rapidly, even from second to second, in response to alteration in posture or the development of tension or relaxation show up most clearly in the multichannel ink-writer type of recorder. What is lost is fidelity of pattern or from frequency limitation is offset by the immediate availability of the record for inspection and study. A combination of both types is ideal and future observations will include both cathode ray inspection and photographs.

Attempts were made to keep the patients as comfortable and relaxed as possible while tracings were being made. Otherwise the results were confused by a varying amount of muscular tension which could be electrically recorded in both arthritic and control subjects. We have also shared the experience of Jacobson[33] that some individuals are difficult or even impossible to relax. Such patients, who made up a very small minority, were discarded from either the arthritic or control groups. Painful and deformed joints were supported in the position of maximum comfort. During the recording the patients were supine or lying on one side, but, while the patellar reflexes were elicited, they were seated with feet supported.

Blocking of the common peroneal nerve was obtained with the infiltration of 2% procaine into the region where the nerve passes across the fibula just below its head. In each case, the block was proven complete and successful by the absence of electrical activity over the anterior tibial muscle when voluntary dorsiflexion of the foot was attempted. In addition, vasomotor and sensory paralysis was evident in the distribution of this nerve.

**Results.** Voluntary contractions were electrically recorded from the extensor and flexor muscles of the forearm while the patient squeezed a rubber bulb. The amount of air expelled from the bulb was recorded on a moving drum by means of a basal metabolism machine. In this way, a rough measurement of the patients' strength (ergogram) could be obtained simultaneously with the electromyograms of the muscles concerned. No consistent deviation was obtained from the recordings of normal controls. At times the electromyographic tracings exhibited an amplitude which was comparable to that obtained from normal individuals, but at times it was decidedly lower. In general, the patients with rheumatoid arthritis tended to relax less readily between squeezes, and the ergographic tracings demonstrated what was apparently marked weakness and rapid fatigability. Both of these findings, however, could be accounted for on the basis of painful and limited finger joints, as well as on muscular weakness or spasm. Tracings from voluntary contractions of other muscles which were associated with arthritic joints of both the leg and arm grossly resembled those from persons without articular disease.

We have mentioned that we were not able to demonstrate either of the 2 outstanding characteristics of spasticity: synchronization of motor unit leads or a spread of tendon reflexes.[29] Two coaxial needle electrodes were inserted into either the quadriceps or triceps muscles of 8 patients with rheumatoid arthritis and repeated gentle voluntary contractions elicited. In every instance, the complete independence of motor unit leads was apparent, a feature which has been well illustrated by Hoefer and Putnam as characteristic of normal individuals without spasticity[29] or rigidity.[30] In 10 patients with rheumatoid arthritis, patellar reflexes were obtained while surface electrodes were placed over the opposite quadriceps and over the forearm muscles. An apparent spread of reflexes was noted

at first, but this was proven to be due to a movement artefact[47] and could be produced in normal individuals. By more careful adjustments of the patient's position and of the recording wires, these artefacts could be eliminated. After such precautions had been taken, although elicitation of the patellar jerks in several of our patients produced such a violent response that the whole body shook, no evidence of a spread could be picked up through the electromyogram.

Next, with the idea that the muscle weakness and atrophy of rheumatoid arthritis might somehow be concerned with involuntary activity rather than disuse,[24] we applied surface electrodes over the muscles of such patients when they were immobile and apparently comfortable and relaxed. In many of them we picked up action currents as shown in Figure 1, *1* and *2*. These tracings are from 2 different patients and represent variations in the rate and amplitude of these regular diphasic spikes. In the first tracing, the rate is 15 to 20 per second, and in the second, 6 per second with amplitudes of 40 and 25 microvolts respectively. We found this pattern in tracings of the muscles obtained with both surface and needle electrodes in 50% (17 out of 34) of the rheumatoid arthritics tested. There was no apparent relationship between the presence or absence of this activity and the age, sex, duration or severity of disease, involvement of the spine or the degree of visible muscular wasting. While such tracings were being recorded, no evidence of muscle activity was apparent to patient or observer. This activity usually appeared and disappeared spontaneously as shown in Figure 1, *2* and *3*. In some patients, it lasted only a few minutes; in 1 we were able to follow it for an hour without change or let-up. In *4*, the disappearance of the activity was obtained by making the patient more comfortable by putting a pillow under a pair of inflamed knees. In *5*, it reappeared again, with the removal of the pillow. In others, however, it persisted in spite of every attempt to increase the comfort and relaxation of the patient. The elicitation of a reflex contraction of the muscle concerned had no effect, either in initiating the pattern, nor, while present, causing its disappearance. Occasionally, the series of regular spikes could be brought out by a voluntary contraction, as in *6*, where one may see a series of voluntary contractions followed by spontaneous activity. Occasionally, they could be abolished by a voluntary contraction, as in *7*, but in general, as shown in *8*, the pattern persisted, no matter how often interrupted by voluntary contractions.

Another characteristic was that the activity might be found at a given time over only one localized area in a large muscle like the quadriceps, when 6 channels were used to record electrical impulses from variously located surface electrodes. On several occasions spontaneous activity was present in 1 muscle related to a joint and not in another. Thus, in respect to a knee joint involved in rheumatoid arthritis, regular diphasic spikes might be obtained from the quadriceps and not simultaneously from the hamstrings, with the reverse true at a later

LEGEND FOR FIG. 1.

FIG. 1.—Involuntary skeletal muscle activity in patients with rheumatoid arthritis, showing influence of discomfort and of voluntary contractions. Surface electrodes. Time recorded at top in seconds. *1*, Regular diphasic spikes obtained from skeletal muscle apparently at rest of patient with rheumatoid arthritis. Rate 15 to 20 per second; amplitude 40 microvolts. *2*, Same as *1*. Rate 6 per second, amplitude 25 microvolts. Spontaneous cessation of activity. *3*, Same as *1* and *2*. Spontaneous disappearance and reappearance of activity. *4*, Disappearance of activity in quadriceps muscle of patient with rheumatoid arthritis of knees when pillow placed under them. *5*, Reappearance of activity in same muscle when pillow removed. *6*, Regular diphasic spikes apparently brought out by voluntary contraction of quadriceps of patient with rhuematoid arthritis. *7* , Activity apparently abolished in same muscle by voluntary contraction. *8*, Persistence of activity in same muscle in face of repeated voluntary contractions.

examination. However, we found no constant relationship of flexor activity with resultant reciprocal extensor inhibition, as has been postulated in explanation of the more common extensor atrophy seen in rheumatoid arthritis.[19] One very interesting finding in a patient with unilateral arthritis was the occurrence of this pattern in the forearm muscles of the as yet uninvolved and asymptomatic side (Fig. 2, *1*). The following week she developed pain and early arthritic involvement of this

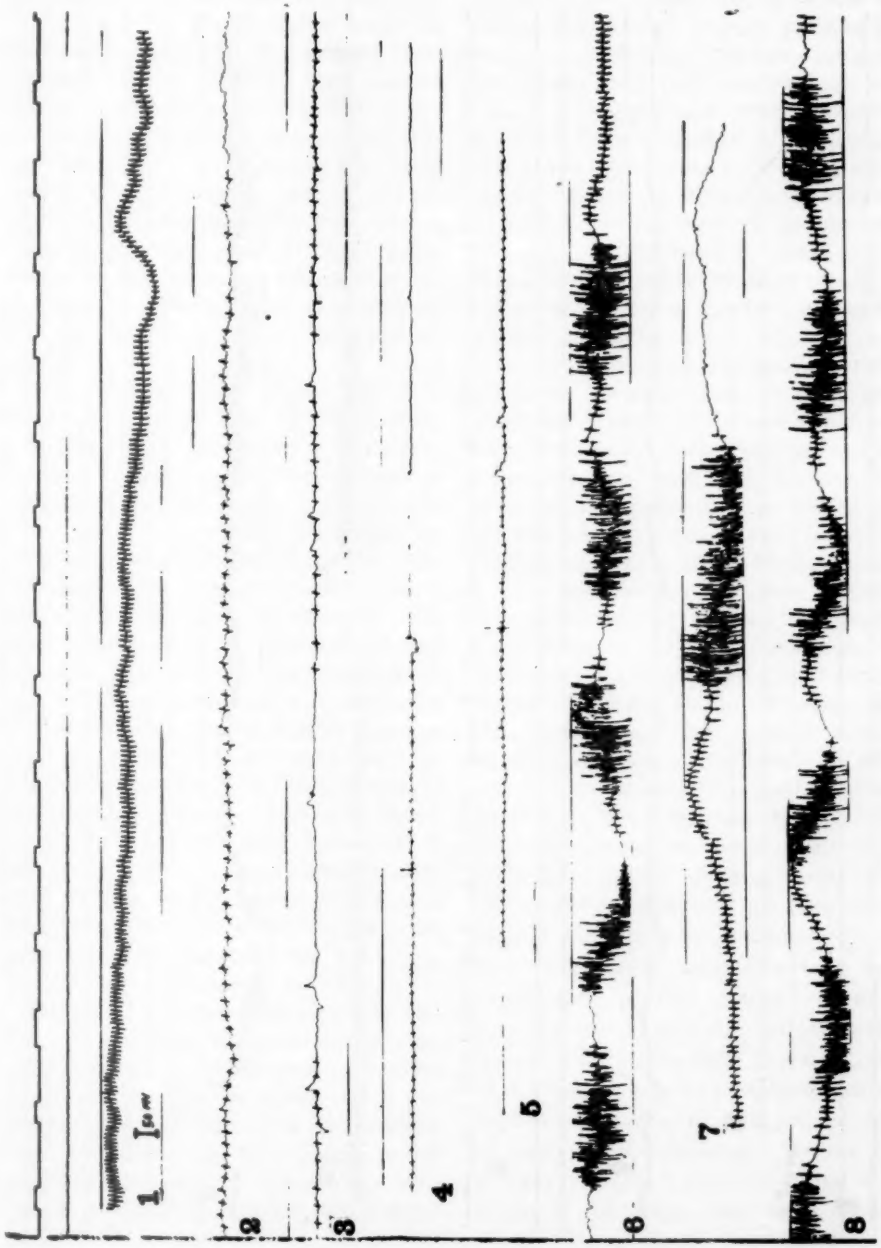


FIG. 1

hand. In this patient, then, disturbed muscle function apparently preceded any clinical evidence of articular disease, an observation which bears out the similar clinical findings of Jones.[34]

Is this spontaneous muscular activity peculiar to rheumatoid arthritis? An example of this same pattern obtained from 2 out of 4 patients with acute specific infectious arthritis (3 gonorrheal and 1 of unknown origin) is shown in Figure 2, *2*. Below, in *3*, we may see the same regular

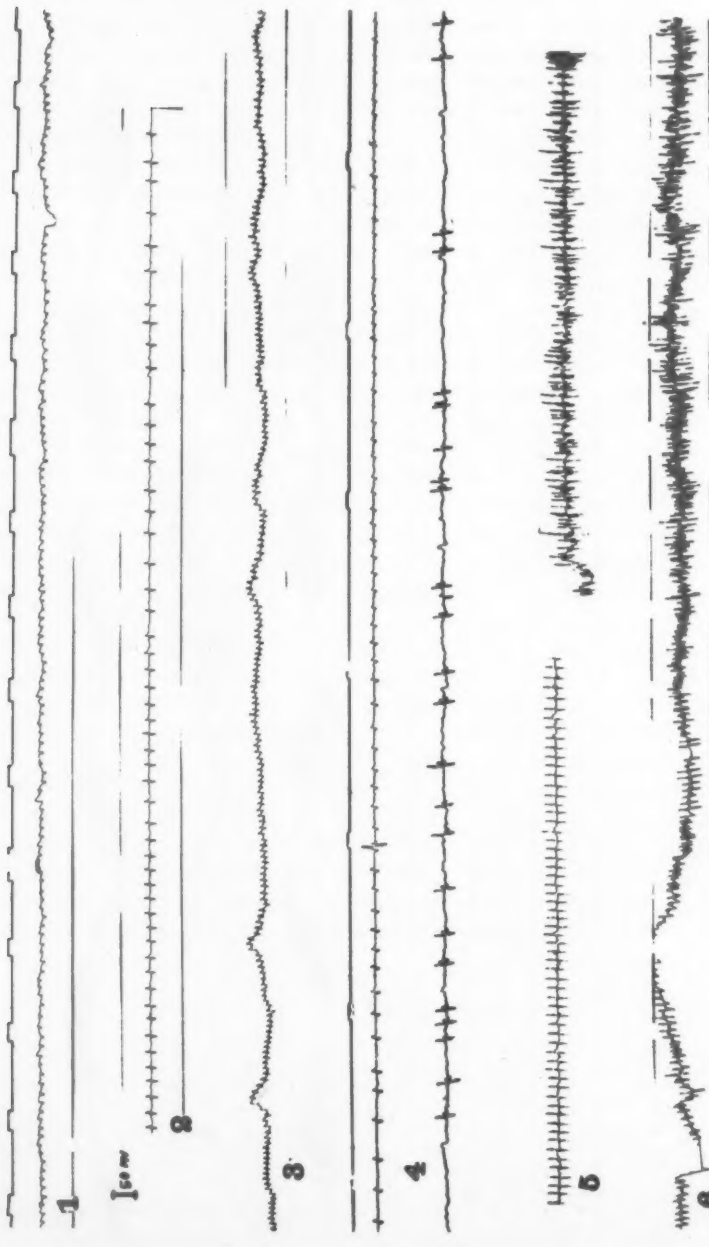


FIG. 2.—Electromyographic tracings of involuntary skeletal muscle activity in rheumatoid arthritis, gonorrheal arthritis, joint fixation and progressive muscular atrophy. Time at top in seconds. *1*, Involuntary activity in the extensor muscles of the forearm, with the related joints as yet uninvolved and asymptomatic. Patient had rheumatoid arthritis of the joints of the opposite arm. Surface electrodes. *2*, Regular diphasic spikes obtained from the biceps of a patient with acute gonorrheal arthritis of the elbow. Surface electrodes. *3*, Similar pattern, recorded from the triceps of a patient with shoulder joint disability due to fixation. Surface electrodes. *4*, Two examples of fasciculations recorded from the muscle of a patient with progressive muscular atrophy. Surface electrodes. (Time directly above in seconds for this tracing only.) *5*, Recording of a *weak* voluntary contraction in a normal subject with needle electrodes. The second half shows the result of increased effort—the usual complex pattern of a voluntary contraction. *6*, Regular diphasic spikes from a resting skeletal muscle of a patient with rheumatoid arthritis merging into a complex pattern as in *5*. Surface electrodes.

series of spikes obtained from the triceps of a patient without any arthritis. This young man had had a lobectomy for bronchiectasis. As part of the postoperative management, his right arm was strapped to his side for 3 weeks and had just been freed. He still had pain on full abduction and rotation of the shoulder. Thus, with the same patterns found in specific infectious arthritis and in joint disability due to fixation, one cannot assign this phenomenon exclusively to the muscles of patients with rheumatoid arthritis. However, in examining the limb muscles of 10 normal controls in an attempt to find activity of this nature, only a few isolated groups of diphasic spikes were observed, nor was involuntary activity present in the muscles of 2 patients with Charcot joints and 1 with dermatomyositis.

Recent observations have shown a closely similar pattern of involuntary discharges to be present in a number of diseases or injuries of the central of peripheral nervous system. In anterior poliomyelitis, spontaneous discharges are a striking feature, especially in the convalescent stage, when they are a sign or improvement in muscle function.[5,60] The same is true of nerve injuries[48,59,61] and infectious polyneuritis[5] with the electromyographic tracings in the 3 conditions resembling each other as well as those we have described in rheumatoid arthritis. The electromyogram is also useful in localizing impairment of muscle innervation from spinal cord lesions, both neoplasms and ruptured intervertebral disks[11,31,59] by means of the recording of involuntary activity in the muscles concerned, with the pattern again resembling that found in rheumatoid arthritis.

The point of origin of the nerve impulses which bring about the spontaneous muscular activity in the diseases or injuries of the nervous system mentioned in the preceding paragraph has not been defined. From the location of the primary pathologic process, it may be assumed to originate in the case of anterior poliomyelitis from anterior horn or internuncial cells and in nerve injuries and infectious polyneuritis from peripheral nerve fibers. When spinal tumors and ruptured intervertebral disks are concerned, however, the activity may be a response to stimuli anywhere along the lower motor neurone or indeed, as pointed out by Hoefer and Guttman,[31] through sensory pathways or from intramedullary structures some distance away from both sensory and motor roots. The application of these concepts furnishes little assistance in the localization of the origin of the involuntary motor activity found in rheumatoid arthritis. The observations outlined in the next paragraph were therefore made, in an attempt to determine to some extent the source of the nerve impulses responsible for this activity.

In 8 patients with rheumatoid arthritis involving the ankle and, or, knee joint, a successful block of the motor and sensory fibers of the common peroneal nerve was performed with 2% procaine. In none of the patients was spontaneous activity present in the anterior tibial muscle following the procaine block, although continuous electromyographic recording was performed for at least 15 minutes. In 5 of the 8, the characteristic pattern which we have described was present before the nerve block. Tracings were also made from the opposite anterior tibial muscle, the nerve supply of which was not interrupted. In 1 patient, activity was present in this muscle both before and after the nerve block. Due to the inconstant nature of these series of diphasic spikes, which, as we have shown, appear and disappear spontaneously, it is difficult to draw conclusions from acute experiments of this nature. However, since the results were so constant in these 8 cases, there seems little reason to doubt that blockage of the peripheral nerve is capable of interrupting the path of origin of these motor discharges. We can thus at least place their source proximal to the point of blockage, but more definite

localization must await further experimentation.

Spontaneous motor activity is found also in other disorders of the neuromuscular system, but in each case the pattern is different from that encountered in rheumatoid arthritis. Fibrillations, which follow denervation of a muscle by section of its motor nerve, can be distinguished from the diphasic spikes which appear with beginning return of function and which, as we have stated, resemble the involuntary activity in rheumatoid arthritis. Both types of activity may sometimes be present at a certain point in the recovery process following nerve injuries.[61] Whether or not such may be the case in rheumatoid arthritis cannot be determined from our observations, since fibrillations are difficult to demonstrate with the ink-writing oscillographs used. The pattern of the muscular activity caused by tetanus toxin[26,58] is also unlike that observed in rheumatoid arthritis, while rigidity associated with extrapyramidal lesions is characterized by irregular electromyographic activity resembling that of a sustained voluntary contraction, although of about one-fourth the average amplitude.[30] Finally, the "rest activity" seen in a certain type of myositis[6] is also similar to the tracing of a moderate voluntary contraction. Thus, the spontaneous muscle activity of rheumatoid arthritis, while resembling closely that found in 4 types of neuromuscular disorders, is unlike that described in the last 4 forms.

The electromyographic pattern of the fasciculations characteristic of progressive muscular atrophy may superficially resemble that of rheumatoid arthritis, as shown by the upper line of Figure 2, *4*. The lower line of this tracing shows a more characteristic run of fasciculations with a more easily recognizable dissimilarity. Another difference lies in the fact that fasciculations may be brought out or intensified by the injection of prostigmine,[15] which was not the case in respect to the spontaneous muscular activity of patients with rheumatoid arthritis. It has been postulated[60] that the differing patterns found in progressive muscular atrophy and in nerve injuries, infectious polyneuritis and anterior poliomyelitis may depend upon the progressive degeneration taking place in the former contrasted to regeneration in the latter 3 conditions. It is of some interest in this respect that tracings recently taken from a patient with rheumatoid arthritis who developed paralysis of dorsiflexion of the foot resembled to a large extent the fasciculations of progressive muscular atrophy. The evidence is conflicting as to the usual point of origin of the fasciculations of progressive muscular atrophy. Experiments utilizing nerve blocking[22,46,50] or interruption[16] have tended to place the origin of the involuntary activity in the distal portion of the nerve, in contrast to our findings in rheumatoid arthritis. It is probable, however, that they may arise at times from any portion of the lower motor neurone, from the cell body to the myoneural junction.[54]

As stated above, sustained involuntary activity was not observed in control patients without arthritis. However, with a concentric needle electrode, which is small enough to pick up the action currents of a single motor unit, it is possible for a normal subject, with a very gentle muscular contraction, to produce a series of spikes as shown in Figure 2, *5*. These may persist, at 9 or 10 to a second, for nearly a minute. With increased effort, the pattern becomes that of a voluntary muscle contraction, as shown in the adjacent tracing. Similarly, the regular series of diphasic spikes from the muscles of an arthritic may merge into a complex pattern indistinguishable from a voluntary muscle contraction (Fig. 2, *6*). This may persist for several minutes without the patient himself being aware of it.

Others have noted[1,21,49] these single-spike discharges of constant height and form recorded in weak voluntary contractions by means of needle electrodes. From their morphology, they have been regarded as recordings of the contractions of a

single motor unit (a group of muscle fibers innervated by a single motor nerve fiber), but of course may represent simultaneous contractions of more than 1 motor unit. With a stronger contraction, more motor units in the vicinity become active and a complex pattern is obtained, in which it is impossible to distinguish the single motor units. In patients with nerve injuries, however, with consequent reduction of a number of active nerve or muscle fibers, a single motor unit pattern of response may be obtained even with maximum efforts.[9,49,51] The tracings from both of these responses resemble quite closely the involuntary muscular activity in patients with rheumatoid arthritis. It seems reasonable then to assume that in this disease there is often only a single motor unit at work in a given area, a situation which the regular series of spikes probably represents. A similar conclusion has been drawn by those who have observed a like pattern of spontaneous activity in anterior poliomyelitis, infectious polyneuritis, nerve injuries and spinal cord lesions.[5,11,31,59,60,61] The reason for this is not clear at present, but 2 possibilities arise by analogy with the recordings of voluntary contractions. The first is that the activity is of a slight degree and utilizes only a single motor unit in a given area, the second that through muscle atrophy the number of active muscle fibers has been reduced in the vicinity of the recording electrode. At present, at least in the case of rheumatoid arthritis, the first possibility seems more plausible, since a full voluntary muscle contraction was possible in all the individuals studied, and since, as we have demonstrated, the single motor unit activity not uncommonly merged into the pattern of a fairly strong muscular contraction. Of course, a combination of the 2 may be at work.

**Histologic Observations.*** We have had the opportunity of examining, postmortem, the central nervous system in 44 patients with rheumatoid arthritis. Since certain degenerative changes of the parenchymatous tissue and proliferative changes of the interstitial tissue are regularly found associated with advancing age alone, a careful comparison was made with a control group of 50 cases of similar age distribution but without rheumatoid arthritis. No specific lesions were found in the brain or spinal cord in the cases with rheumatoid arthritis, but alterations usually attributed to aging were more pronounced than in the controls. The histologic alterations in both arthritics and controls included degeneration and diminution in number of anterior horn cells, loss of axons and their myelin sheath in various regions of both white and gray matter, and a concomitant gliosis replacing this loss of parenchymatous tissue. As far as could be ascertained, no lesion of the upper motor neurones was present, a finding in accordance with the electromyographic observations.

The anterior horn cell changes consisted largely of 3 types of degeneration. *Chronic shrinkage* in which the cell body was reduced in size, the nucleus pyknotic, the tigroid substance clumped and hyperchromatic and in which the cell was accompanied by few, if any, satellites, was the most common nerve cell alteration. *Pigmentary atrophy* was next most frequently found and this disease was characterized by increase in lipofuchsin with a loss of Nissl substance. Sometimes the cell was apparently increased in size with an eccentric nucleus, and the cell membrane, bulging outward, was filled with bright yellow pigment in the Nissl stain, while only a very few tigroid bodies remained. Such a cell was often accompanied by a ring of satellites, chiefly oligodendroglia, and neuronophagia was sometimes encountered. A very common finding was glia nodules, small scars of glia presumably marking the sites of former nerve cells. These 2 types of anterior horn cell disease are usually regarded as primary degenerations. They were found

* One of the authors, Dr. L. R. Morrison, will report in detail elsewhere on the histologic examination of the neuromuscular system in rheumatoid arthritis.

in the mesial cell groups that control the musculature of the trunk, and more particularly in the lateral groups wherein are located the cell bodies of the nerves that innervate the muscles of the limbs. A third type of cell disease, *retrograde degeneration*, was found principally in the lateral projections of the anterior horns and only in the arthritic group. This lesion consisted of swelling of the cell body, central chromatolysis with peripheral pyknosis, occasionally vacuolation, and, very often, eccentricity of the nucleus. Examples of this "axonal reaction" were found in one-fourth of the 44 cases.

Anterior horn cell changes in rheumatoid arthritis have been described by previous workers, although in no instance has comparison been made with a control group. The earliest report encountered is that of Folli[13] in 1893, followed by Bannatyne[3] in 1898, Mott and Tredgold[39] in 1902 and by Penny[41] in 1913, who made careful and detailed observations on anterior horn cell alterations in 6 cases.

Changes were also observed in our patients in the white matter, including loss of myelin, disease and disappearance of axons and hyperplasia of astrocytes, but they were not greater than could be ascribed to advancing age. The same can be said of the alterations in Clarke's column, in contrast to the anterior horn cell degeneration, which, while not specific, was definitely more advanced than in the control group.

In the peripheral nerves, lesions were found somewhat similar to those described by other investigators.[3,12,17,18,20,39,41,45,53] In 26 out of 31 cases, inflammatory reactions were present in the nerve sheath, chiefly in the perineurium. The reaction consisted largely of lymphocytes and plasma cells with endothelial and occasional epithelioid cells or monocytes present as well. Sometimes, as emphasized in recent reports,[17,18,53] these foci were nodular in appearance (Figs. 3 and 4), and had an indefinite, acellular center, at times resembling collagen. The eosinophilic central region did not show fibrinoid degeneration, however, and neither was there any conspicuous reaction of epithelioid cells. A fairly dense zone of lymphocytes would often surround the acellular center while plasma cells and monocytes were more apt to be found at the periphery. There was no fibroblastic capsule surrounding the outer layer but a fairly sharp line of demarcation was brought about by the interstitial tissue of the nerve, either the perineurium, or, less commonly, the epineurium. More frequently, however, the zones were less clear-cut and the lesions looked less nodular, being sometimes long and narrow with lymphocytes and plasma cells more or less intermingled and the inflammatory reaction often situated in relation to a blood-vessel. In addition to these paravascular collections of reacting cells, there were occasionally other groups, chiefly lymphocytes, found in relation to the endoneurium, too small to have any definite shape yet conspicuous enough to be called pathologic and not found in normal nerves.

While these lesions were not ordinarily in direct relation to the parenchymatous structures, the various nerve sheaths being interposed, the myelin sheaths and the axons often showed pathologic changes. These changes, while distinct enough, were of a scattered, isolated distribution without widespread patches of nerve degeneration. Usually the axons and medullary sheaths were affected individually or in small groups, commensurate with the small size and number of the perineuritic foci. Silver impregnations were not done on some of the cases, but on those on which they were done 16 of them showed alterations of the axons ranging from thickening through moniliform swellings up to vacuolation, fragmentation and tortuosity (see Figs. 5 and 6).

Alterations in the myelin sheath, while not extensive nor always present, were seen in the Oil Red O and the Weigert or Weil stains. They also varied in degree from slight thickening and pallor to complete myelin breakdown, with myelin figure formation, gitter cell activity and

frank patches of demyelination (Fig. 7). This disease of the myelin was evidently of a progressive nature, for in some cases of long standing, severe arthritis, there was increased connective tissue stroma in the nerve preparations, yet at the same time fat-laden phagocytic cells were still active.

On account of the disease of the axons of the peripheral nerves, there were certain axonal reactions, or retrograde degenerations, in the corresponding nerve cell

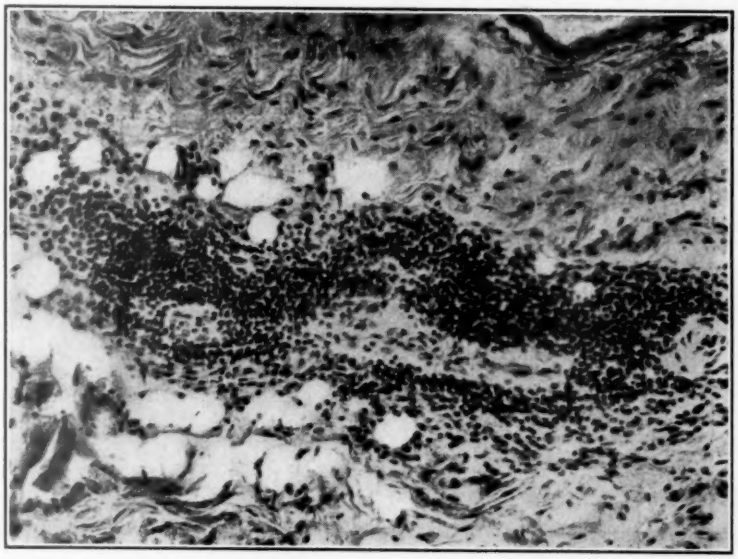

FIG. 3.—Longitudinal section of peripheral nerve showing nodular inflammatory reaction in nerve sheath. Hematoxylin and eosin stain. × 100.

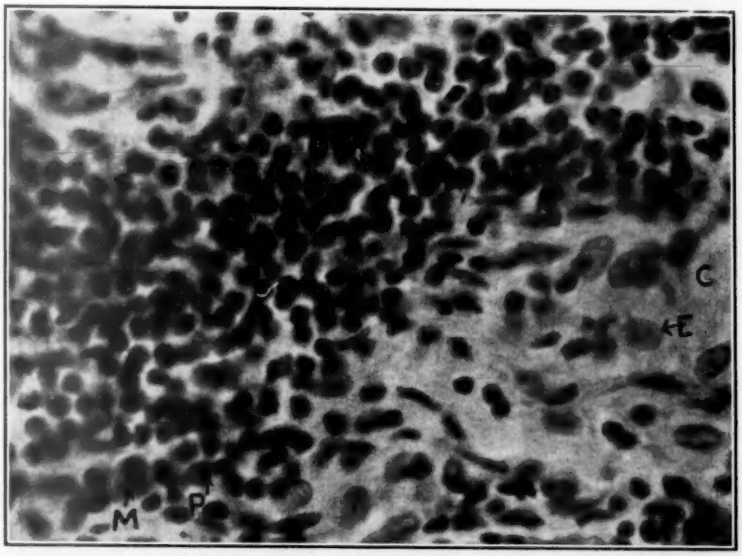


FIG. 4.—Detail from Figure 3 showing relatively acellular center (*C*), endothelial cells (*E*), lymphocytes, plasma cells (*P*) and monocytes (*M*). Hematoxylin and eosin stain. × 400.

bodies. Those of the anterior horn cells have already been mentioned but there were in addition somewhat similar alterations in several of the small number of posterior root ganglia we have examined. These posterior root ganglion cells showed swelling, central chromatolysis, neuronophagia, increased capsule cells and, in at least 1 case (an 8 year old boy), marked increase in melanotic pigment. Identical changes are recorded by Penny[41] in his histologic study of 6 cases in 1913. Also,

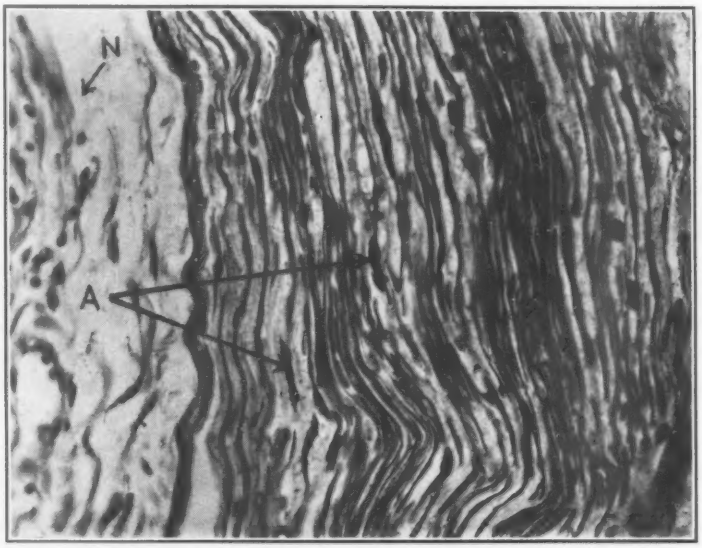


FIG. 5.—Swelling and thickening of axons (*A*) in close proximity to perineural nodule, edge of which is visible (*N*). Bodian stain. × 300.

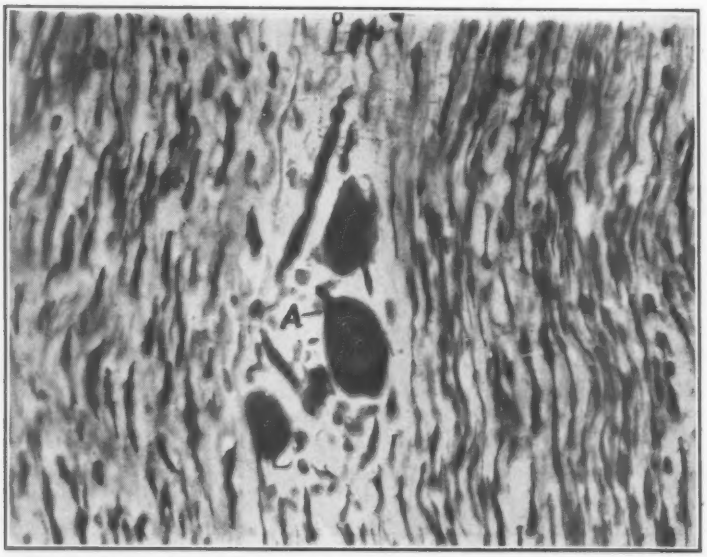


FIG. 6.—Swollen argentophilic fragments of axon (*A*). Peripheral nerve. Bodian stain. × 300.

as might be expected, alterations were sometimes found in anterior and posterior roots as a possible cause of, or consequent to the degeneration in the corresponding cell bodies. Previous studies have included these findings.[13,39,45,55,57] In a few instances ganglia of the sympathetic chain were examined, but the excessive pigmentation and interstitial infiltration occasionally seen may have been due solely to age, according to the standards of Kuntz.[35]

As already reported by others,[7,8,14,20,43,52,53] alterations were also found in skeletal muscles. These consisted in collections of lymphocytes, plasma cells and, in the

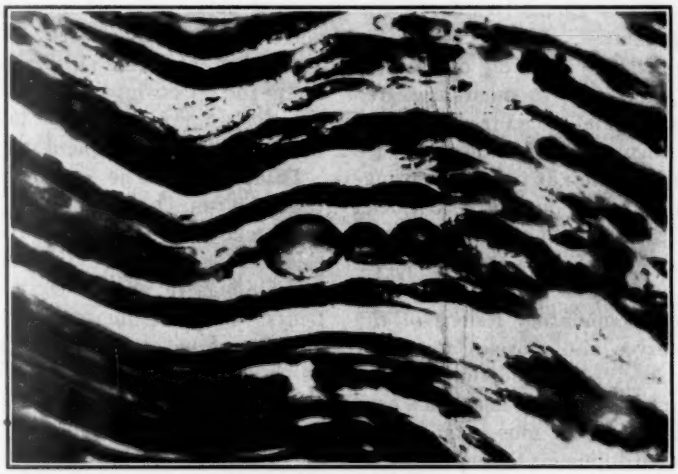

FIG. 7.—Swelling of the myelin sheath with myelin figure formation. Peripheral nerve. Weil stain. × 300.

FIG. 8.—Muscle from right calf showing paravascular inflammatory nodule, which consists chiefly of lymphocytes and plasma cells. Eosin-methylene blue stain. × 100.

larger foci, occasional epithelioid cells. Such lesions were in the perimysium or endomysium and occurred in 8 out of 14 cases. The lesions varied from definite nodular forms (Fig. 8) to smaller collections of lymphocytes and plasma cells often seen in relation to a blood-vessel. In addition to the inflammatory reaction in the interstitial tissue of the muscle, the muscle fibers themselves were frequently degenerated. This degeneration was characterized by thinning of the muscle fibers, sometimes to such a degree that the sarcolemmal nuclei from opposite sides were touching one another; increase in sarcolemmal nuclei; at times the formation of dense cords of pyknotic nuclei clustered in the midst of a pale, shrunken muscle fiber; loss of cross-striations and increase in connective tissue.

While the inflammatory lesions of the peripheral nerves and muscles suggested specificity, closely corresponding lesions were found in muscle and a nerve in a case of dermatomyositis, in muscle in 1 case of disseminated lupus erythematosus and in a nerve in another, and in muscle from a case of scleroderma. Two patients with rheumatic heart disease, and without evidence of arthritis at autopsy, showed inflammatory changes in peripheral nerves. Since other investigators have reported inflammatory lesions similar to those of rheumatoid arthritis in the muscles in dermatomyositis,[4] scleroderma,[4] rheumatic fever,[7] disseminated lupus erythematosus[43] and anterior poliomyelitis,[12] the existence of characteristic, diagnostic, histologic changes in the neuromuscular system in rheumatoid arthritis remains to be demonstrated.

The results of our histologic studies of the nervous system and muscles in rheumatoid arthritis, combined with those reported in the literature, furnish, however, further evidence of the systemic nature of the disease. Direct involvement of the neuromuscular system by the disease process seems highly likely in the case of peripheral nerves and muscles and possibly accounts for the unexpected degree of degeneration present in the anterior horn cells. In addition, a reasonable basis is now at hand to explain either wholly or in part the motor and sensory neurologic manifestations of rheumatoid arthritis, as well as the spontaneous skeletal muscle activity demonstrated by electromyographic tracings. Material for histologic examination is available from only 2 patients in whom such muscular activity was demonstrated. Both showed at autopsy, performed $3\frac{1}{2}$ years and 1 year after the electromyographic studies respectively, inflammatory lesions of a muscle and of a peripheral nerve.

**Discussion.** The general agreement that the muscles of normal individuals in a relaxed state show no evidence of electrical activity[1,28,33] is confirmed by our findings in normal controls. In patients with rheumatoid arthritis, the muscles related to the involved joints may be in an inconstant state of tension. From the nerve-blocking experiments, it is probable that this tension is not produced within the muscle fibers or at the neuromuscular junction but by motor impulses from above the point of block. An additional observation is that there is often only a single motor unit at work in a given area. We have thus far no means of knowing whether or not this tension arises reflexly in response to stimulation of the articular sensory nerve endings. The activity was only rarely associated with conscious discomfort on the part of the patient, and could not be produced by causing pain in the involved joint by squeezing or moving it. Of course the extreme form of this tension, the palpable muscle spasm "guarding" a painful joint has always been assumed to arise reflexly, chiefly because it disappears when the pain is relieved and because of its similarity to muscle spasm arising from disorders of thoracic or abdominal viscera.

The explanation of muscular atrophy in arthritis is not yet at hand, although the theory suggested by Sir James Paget[40] in 1873 that it arises reflexly from painful

stimuli has received the greatest support in several comprehensive reviews of the subject.[2,23,36] Furthermore, it has been shown by animal experiments[10,25,32,44] that muscle atrophy can be prevented or diminished by cutting the posterior roots which carry impulses to the cord from joints in which a chemical or infectious arthritis has been set up. The lack of knowledge of the mechanism by which the muscle atrophy takes place in consequence to the stimuli arising in the joints presents the real difficulty in the full acceptance of this theory. Harding[23] has suggested that it is due to muscular overactivity from abnormally excitable spinal centers and has found increased oxygen consumption in the muscles atrophying sequential to the arthritis. The constant purposeless activity called fibrillation has been brought forward as the cause of muscle atrophy following denervation,[56] although this hypothesis also remains unproven. The muscular tension which we have found in our patients must be present many hours out of the 24. It might conceivably be related, though yet unproven and by a mechanism not explained, to the development of muscular atrophy. However, the existence of continued single motor unit discharges would mean that the tension produced is well below the range of fatigue of the units at work. It is therefore doubtful that muscle wasting could be caused by such activity as we have described.

In view of the demonstration of lesions in the neuromuscular system of patients with rheumatoid arthritis, a more plausible explanation of the spontaneous muscular activity may be available. If we accept this explanation, our nerve-blocking experiments would tend to place their origin somewhere in the proximal part of a lower motor neurone rather than in a muscle, neuromuscular junction or the distal portion of a peripheral nerve. Such a concept is borne out by the finding of a closely similar pattern of single motor unit activity in disorders involving chiefly the lower motor neurone, including anterior poliomyelitis, nerve injuries and infectious polyneuritis.

One objection to this concept lies in the fact that we have recorded single motor unit activity from the muscles of patients with specific infectious arthritis and joint disability due to fixation, where there is no reason to believe that pathologic changes take place in the nerves or muscles similar to those in rheumatoid arthritis.[14] Such patients also demonstrate a rapid onset of muscle weakness and atrophy. Just as the single motor unit muscular activity in lesions of the spinal cord is believed to arise at times reflexly through sensory pathways, it is entirely possible that the activity of like pattern in rheumatoid arthritis may also result from sensory impulses set up in the inflamed joints. This second explanation would also fit in with the results of our nerve-blocking experiments.

It would be premature at this time to attempt to draw any final conclusions as to the relationship between muscle activity, weakness or atrophy and the histologic changes found in the nerves and muscles in rheumatoid arthritis. We shall be satisfied if this presentation and discussion of our findings will encourage the increasing interest in the importance of the neuromuscular system in the total clinical picture in rheumatoid arthritis.

**Summary.** 1. In an attempt to elucidate the mechanism of muscle weakness and atrophy in rheumatoid arthritis, electromyographic studies were performed on patients with rheumatoid and other forms of arthritis. In addition, postmortem histologic observations were made of the central and peripheral nervous system and of the muscles in rheumatoid arthritis.

2. Tracings of voluntary muscle contractions showed no constant deviation from those of normal controls.

3. Synchronization of motor unit leads and spread of tendon reflexes, important electromyographic characteristics of upper motor neurone lesions, could not be demonstrated in patients with rheumatoid arthritis.

4. Involuntary skeletal muscle activity was inconstantly present in 50% of 34 patients with rheumatoid arthritis, consisting usually in a series of regularly recurring diphasic spikes, believed to represent contractions of a single motor unit. A closely similar pattern has been observed in anterior poliomyelitis, peripheral nerve injuries, infectious polyneuritis and spinal cord lesions (tumors and ruptured intervertebral disks).

5. In 8 patients, regularly recurring spikes were not recorded after procaine block of the motor nerve supply to the muscle examined. This finding places their origin above the point of block.

6. In 44 patients with rheumatoid arthritis, the central nervous system showed no specific lesions at postmortem. Alterations usually attributed to aging were more pronounced, however, in the arthritics than in a control group of similar age distribution. These changes were found especially in the lateral projections of the anterior horns.

7. Lesions were found in the peripheral nerves (in 26 out of 31 cases) and in the muscles (in 8 out of 14 cases) similar to those reported by other observers.

8. Direct involvement of the neuromuscular system by the disease process seems highly likely in rheumatoid arthritis and may explain the neurologic signs and symptoms so prominent in this disease, including muscle weakness and atrophy.

9. The spontaneous skeletal muscle activity in rheumatoid arthritis may also be explained on the basis of pathologic lesions of the lower motor neurones, with corroborative evidence furnished by the closely similar electromyographic pattern found in known disorders of this portion of the nervous system.

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# PERSISTENCE OF PENICILLIN IN THE CEREBROSPINAL FLUID AFTER MASSIVE INTRAVENOUS ADMINISTRATION

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The fact that penicillin can surmount the hemato-encephalic barrier and appear in significant concentrations* in the cerebrospinal fluid was recently demonstrated in a previous publication.[3] It was found that patients receiving 10 million units of penicillin, intravenously, over a 24 hour period, exhibited penicillin in the cerebrospinal fluid in 71.5% of the series, whereas patients receiving 25 million units, intravenously, revealed significant amounts of the drug in 100% of the cases. It was also found that as the dose of the drug was increased, the penicillin level in the cerebrospinal fluid was likewise increased.

In the above study, however, all determinations of spinal fluid concentration of penicillin were made on fluids which had been drawn within ½ hour after completion of intravenous therapy.

The question, "How long does the penicillin remain in the cerebrospinal fluid?" immediately came to mind. The following study was done to ascertain the duration of time over which penicillin could be detected in cerebrospinal fluid following the intravenous administration of 25 million units of penicillin over a 24 hour period.

A group of 83 patients exhibiting dark-field positive lesions of primary or secondary syphilis was included in this study. Twenty-five million units of penicillin, contained in 1000 cc. of physiologic saline solution, were administered to each patient by the intravenous route, using drip technique. The pinch clamp was adjusted so that delivery of the 1000 cc. of solution containing the penicillin was distributed equitably over the 24 hour period. A subcutaneous injection of 300 mg. heparin, contained in the "Pitkin menstruum,"[1] was given immediately prior to the initiation of penicillin therapy to circumvent the thrombophlebitis so frequently associated with intravenous administration of penicillin.

A lumbar puncture was performed on each patient only once after the conclusion of therapy. One group of 3 patients was subjected to lumbar puncture 18 hours after the conclusion of penicillin therapy. Another group of 14 patients was studied 12 hours after therapy. Thereafter, additional groups of 14 patients each were examined at 9, 8, 7 and 6 hours after the discontinuation of therapy. A smaller group of 10 patients was examined 5 hours after the completion of therapy, inasmuch as our supply of penicillin was exhausted at this point.

The results of this study are set forth in Table 1. No penicillin could be recovered from patients either at 18 or at 12 hours after completion of treatment.

At 9 hours, however, 1 of the 14 patients

* Significant levels for the purposes of this paper are 0.01 to 0.078 unit per cc. as reported by McDermott, Benoit and DuBois[2] to be the "effective level" for *Treponema pallidum*.

studied revealed a significant level. Thereafter, as the interval between the time of completion of treatment and the time of lumbar puncture was shortened, the frequency of appearance of appreciable penicillin levels varied inversely. Thus, at 5 hours, 100% of the patients studied demonstrated significant cerebrospinal levels of penicillin.

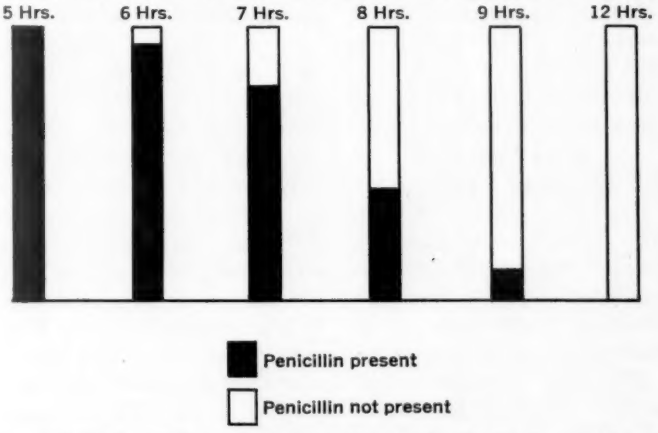
tions of the nervous system is generally recognized. A safe, effective mode of directing the drug to the site of the pathologic process, therefore, assumes great importance, and it follows that the length of time over which the drug will remain at the site desired is of great moment.

No relationship could be established between age, weight, or sex in either the

TABLE 1.—PENICILLIN LEVELS IN CEREBROSPINAL FLUID AFTER TREATMENT
OXFORD UNITS PER CC.

| 5 hrs. | 6 hrs. | 7 hrs. | 8 hrs. | 9 hrs. | 12 hrs. |
|---|---|---|---|---|---|
| 0.04 | 0.02 | 0.1 | 0 05 | 0 | 0 |
| 0.06 | 0.025 | 0 | 0 | 0 | 0 |
| 0.025 | 0.06 | 0 03 | 0 | 0 | 0 |
| 0.05 | 0.06 | 0 | 0 | 0 | 0 |
| 0.06 | 0.03 | 0.03 | 0 | 0 | 0 |
| 0.1 | 0.06 | 0.02 | 0.025 | 0 | 0 |
| 0.05 | 0.1 | 0.025 | 0.05 | 0 | 0 |
| 0.05 | 0.1 | 0.1 | 0.025 | 0 | 0 |
| 0.3 | 0 | 0.05 | 0 | 0 | 0 |
| 0.03 | 0.04 | 0.05 | 0 | 0 | 0 |
| | 0.025 | 0.025 | 0.025 | 0 | 0 |
| | 0.02 | 0.025 | 0 | 0 | 0 |
| | 0.05 | 0 | 0.025 | 0 | 0 |
| | 0.04 | 0.03 | 0 | 0.02 | 0 |
| | | *Percentage of Fluids Showing Penicillin* | | | |
| 100% | 93% | 78% | 43% | 7% | |

TABLE 2.—RELATIONSHIP BETWEEN TIME FOLLOWING COMPLETION OF TREATMENT AND FREQUENCY OF DETECTION OF PENICILLIN IN CEREBROSPINAL FLUID




Each group comprises 14 patients with the exception of the "5 Hrs." group in which there were 10 patients.

Table 2 graphically illustrates the relationship between the length of time elapsing following the completion of therapy and the frequency of detection of penicillin in the cerebrospinal fluid.

**Comment.** That penicillin is a most effective agent in the treatment of infec-

concentration or the frequency of appearance of penicillin in the cerebrospinal fluid after given periods of time, following completion of therapy.

**Summary.** 1. A group of 83 patients with dark-field positive syphilis were given

25 million units of penicillin by continuous intravenous drip over a 24 hour period.

2. Penicillin activity in the cerebrospinal fluid of these patients was determined at 18, 12, 9, 8, 7, 6 and 5 hours after completion of treatment.

3. Penicillin could be detected in the cerebrospinal fluid of all patients whose lumbar puncture was performed 5 hours after completion of treatment; the highest levels being 0.3 Oxford units per cc., and the lowest being 0.04 Oxford units per cc.

4. Inverse proportion was observed between time elapsed after completion of treatment and percentage of patients presenting penicillin in the cerebrospinal fluid.

5. No penicillin was detectable in the cerebrospinal fluid of patients 12 hours after the completion of treatment.

We are indebted to Mr. John L. Smith of Charles Pfizer & Co., for his keen interest, valuable suggestions and constant coöperation. We were able, through him, to obtain the generous supply of penicillin utilized in these experimental studies. We wish to express our appreciation to Miss Helen Zaborowski for technical assistance.

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# TWO COEXISTENT STRAINS OF VIRIDANS STREPTOCOCCUS ISOLATED FROM BLOOD CULTURES BY PENICILLIN SENSITIVITY TESTS*

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The advent of penicillin therapy in the treatment of subacute bacterial endocarditis should have a salutary effect in stimulating more careful bacteriologic studies of the organism. With increased experience in the effective use of penicillin to achieve clinical cures in these cases, it now seems of paramount importance to investigate more critically the possible reasons for the reappearance of bacteria during, or shortly after completion of, treatment presumed to be adequate. Most of the larger series of cases have included a small percentage falling into this group, which have frequently yielded to increased therapy. Two possible reasons have been considered from time to time in the literature: (1) the development of an acquired resistance to penicillin by the particular strain involved; (2) the possible presence of more than 1 strain at the time of treatment. The first has received wide, and on the whole uncritical, acceptance; the second has only occasionally been suggested, most recently by MacNeal and Blevins.[4] Believing that the latter possibility has not received the careful consideration it warrants, we submit the following report of 2 coëxistent strains of streptococci with widely divergent sensitivities to penicillin, found in each of 2 successive blood cultures drawn from a recent patient with subacute bacterial endocarditis.

The first evidence of 2 strains was observed in the course of a rapid estimate of sensitivity to penicillin routinely done in this laboratory by placing filter paper disks impregnated with known dilutions of a penicillin standard on blood agar plates thinly streaked with the first identifiable growth obtained. Since the original culture had taken 72 hours to develop in broth flasks, and subculture growth on blood agar plates was scanty, duplicate test plates were made; 1 for routine aërobic culture at 37° C., 1 for 10% $CO_2$. In 24 hours the culture under reduced oxygen tension had grown well, outside of a sharply defined clear zone surrounding the filter paper disk, which indicated a sensitivity of 0.03 Oxford units. Normal aërobic incubation had only produced a scanty, irregular growth in the outer areas of the second test plate at this time. Both plates were returned for further incubation under normal oxygen tension. Careful examination after 48 hours revealed similar, well-defined zones of inhibition now clearly apparent on both plates, and in addition 2 and 3 single colonies, respectively, growing at various points well within the clear zones.

Subcultures from these isolated colonies grew luxuriantly in 24 hours under normal atmospheric conditions. The simultaneous subcultures made from the first growth observed, selected just beyond the edge of the clear zone to minimize any differences due to unequal exposure to penicillin, again required 10% $CO_2$ for optimal growth in 24 hours. Blood agar plate sensitivities to penicillin were repeated for each of the 2 strains thus isolated. The colonies subcultured from outside the zone of inhibition again had a sensitivity of 0.03 Oxford units, and will hereafter be referred to as the C–PS strain. In marked contrast, the paper disk method indicated a probable sensitivity of 5 Ox-

* Aided by a grant from the A. B. Kuppenheimer Fund.

ford units for the second strain, subcultured from the scattered colonies within the original clear zone. The latter will be referred to as the C–PO strain. Both sensitivities were subsequently confirmed by a turbidity method. Blood agar plate sensitivities, repeated with each strain on several occasions, failed to produce any variation in the growth characteristics or sensitivity of either one, or any other colonies within the clear zone of the C–PS strain which might suggest the development of a penicillin resistant variant of the original strain. The 2 strains were similarly isolated from a second culture, taken 24 hours later.

Cultural and biochemical evidence further confirmed our impression of the presence of 2 distinct strains, and the differential characteristics remained unchanged over a period of 3 months, except for relatively greater ease in growing the C–PS strain due to prolonged subculture on artificial media. Both strains produced alpha hemolysis on (human) blood agar plates, and could be roughly classified as belonging to the viridans group of streptococci, although each had a distinctively different appearance. The C–PS strain consistently produced a flat, dark forest-green growth. Under the colony scope this resolved itself into very small, discrete, smooth, moist, pyramidal colonies, dark in color, and surrounded by a fairly extensive area of deep green discoloration with partial destruction of the erythrocytes. The C–PO strain was equally consistent. Larger colonies, smoothly rounded, glistening, paler yellow-green tending toward confluence, and a moderate area of discoloration without visible destruction of the erythrocytes were formed, which browned somewhat with age. Further pertinent data can be summarized as follows: dextrose, lactose, maltose, mannite, salicin, sucrose were fermented in 24 hours by the C–PO strain. The C–PS strain fermented none in a week, although good growth was supported by the medium. Neither attacked inulin in 1 week. Medium for optimum growth of the C–PO strain was ascites-dextrose-vea broth, although a simple veal broth supported it adequately. The C–PS strain continued to require Brewer's medium for optimum growth.

Lancefield typing sera were not available to us at the time of this study, and the C–PS strain spontaneously failed to survive routine subculture after 3 months. However, the diversity of the action on blood agar, sensitivity to penicillin, and sugar fermentation reactions appear to be sufficient to fulfill Sherman's criterion that "a difference in 5 characters is ample to tell us that 2 bacteria are not the same."[5] No further positive blood cultures were obtained, as high dosage penicillin therapy, based on the indicated sensitivities, was immediately instituted, the patient became bacteria-free, and has remained so to date (11 months). Because of the preponderantly heavy growth of the C–PS strain, we were not successful in isolating the individual strains by any other means than the difference in sensitivity to penicillin.

Since the early work of one of us[3] in isolating 2 coëxistent strains of viridans streptococcus from the same heart valve lesions, we have been interested in the incidence of mixed infections in septicemia and bacterial endocarditis. We feel that the simultaneous presence of more than 1 strain of streptococcus is quite possible, and a definite factor to be considered in the bacteriologic diagnosis of subacute bacterial endocarditis. Fleming introduced the principle of sensitivity to penicillin as a differential factor in isolating different organisms in 1929, in his work with *H. influenzæ*.[2] Within the past few years it has been rather widely developed as a means of securing positive cultures for the diagnosis of pertussis. The use of penicillin directly on the culture plate for this purpose has most recently been discussed by Bradford, Day and Berry[1] but so far as we have been able to determine this is the first application of the principle to the isolation of 2 infectious strains of streptococcus occurring

simultaneously in a case of bacterial endocarditis. Such a condition is particularly important when a heavy or antagonistic growth of a relatively sensitive strain may completely mask the presence of a more resistant strain, unless positive cultures are carefully studied with this in view. Should oversight lead to inadequate penicillin therapy, clinical relapse with reappearance of the more resistant strain could be expected.

**Summary.** 1. Two coëxistent strains of *Strep. viridans* were isolated from a case of subacute bacterial endocarditis only because of widely divergent sensitivities to penicillin.

2. The undiscovered presence of more than 1 infective strain of streptococcus can be a factor in causing apparent relapse of patients with subacute bacterial endocarditis, following penicillin therapy.

3. The Oxford cup, or filter paper disk modification, for determining penicillin sensitivity may provide a valuable method for isolating individual strains of organisms from a mixed culture.

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# THE SPONTANEOUS OCCURRENCE OF NEW BACTERIAL INFECTIONS DURING THE COURSE OF TREATMENT WITH STREPTOMYCIN OR PENICILLIN*†

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The use of antibiotic agents with highly specific, selective activity has solved many of the difficulties encountered in the treatment of infectious diseases. However, many new problems have been created; some of these arise because the lives of patients are prolonged sufficiently to allow time for the development of complications of the original disease; others are the result of accidents occurring during the administration of these drugs, such as the introduction of new bacteria; some arise as the result of the use of a drug with no action against the infecting organism. It is with one of these problems, the appearance of new infections during the course of treatment with such agents as penicillin and streptomycin, that this paper concerns itself.

Although both penicillin and streptomycin are highly antibacterial, this activity is more or less specific; thus, penicillin is active mainly against gram-positive bacteria, whereas streptomycin exerts its greatest effects against members of the gram-negative group. Although organisms susceptible to each of these agents show varying degrees of resistance, on the whole most of the susceptible bacteria can be eliminated if an adequate dose of either of the antibiotic agents is given. During the course of therapy with streptomycin or penicillin, in addition to an effect on the specific organism responsible for an infection, alterations in the bacterial flora in various parts of the body may occur; thus gram-positive bacteria may be eliminated from the nasopharyngeal flora when penicillin is administered and gram-negative ones when streptomycin is given. Lipman, Coss and Boots,[1] in a study of the throat and intestinal flora of rheumatoid arthritis cases to whom penicillin was administered daily over a period of months demonstrated a rapid and striking change. The throat cultures of all of the patients revealed a predominance of gram-positive diplococci sensitive to penicillin prior to antibiotic therapy. During the course of treatment, gram-negative organisms, mainly *E. coli*, were found to be predominant. Less striking though definite changes in the intestinal flora also took place.

It is possible that such alterations in the distribution of organisms in sites of the body where a mixed flora is usually present may occur in many patients who receive therapy with one of the specific antibiotic agents. In most cases, such changes in the bacterial population with suppression of certain groups of bacteria and increase in the number of others probably leads to no untoward result, and the patient's recovery is not affected. In other cases, however, such alterations in the flora result in the rapid growth of virulent bacteria, which may have been present originally only in very small numbers, and which were not susceptible to the antibiotic agent administered. If the general resistance to infection be depressed, new infections may occur following such a change. In the cases described below, the use of either streptomycin or penicillin resulted in the elimination of one group of bacteria and allowed another which was probably present in small numbers in certain sites to become numeri-

* The streptomycin used in this study was provided by the National Research Council from supplies allocated to it by the Civilian Production Administration for Clinical Investigation recommended by the Committee on Chemotherapeutics and Other Agents.

† This study was aided by a grant from the Johnson Research Foundation, New Brunswick, N. J.

cally predominant and to invade the tissues and produce new disease.

New infections arising during the course of antibiotic treatment may have a different pathogenesis than the one just described. Organisms that are not susceptible to the specific agent being used may be introduced accidentally (from the skin or from contaminated apparatus) during the administration of the antibiotic substance into the pleural, peritoneal, synovial, or lumbar spaces or into the muscles or blood stream in the course of venipuncture and intramuscular injections, and may produce new infections at a time when the original disease is responding well to therapy. Infection with gram-negative bacteria during the course of penicillin treatment, such as gluteal abscess due to *E. coli* and infections of pleural fluids with *Ps. æruginosa* or with *P. vulgaris*, have been seen in this hospital. This type of new infection is not the result of a change in the normal bacterial flora of tissues, however, but results from the introduction of new organisms accidentally during the manipulations incident to the proper administration of the antibiotic agents. This type of new infection is not described in this paper. Only those cases in which alterations in the normally occurring bacterial flora led to the establishment of new infections are discussed.

In our study of the treatment of scarlet fever with penicillin, Type B and untypable strains of *H. influenzæ* that could not be detected on the original nasal and pharyngeal cultures became the predominant organism in the nasopharynx of a large number of patients after *Strep. pyogenes* had been eradicated. This was probably due to the fact that there was an increase in the carrier rate of *H. influenzæ* in this part of the country during the past winter as evidenced by detection of a larger number of individuals harboring this bacterium and by an increase in the incidence of *H. influenzæ* meningitis. The failure to isolate this organism from the throat cultures before penicillin was administered was probably due to the fact that they were present only in very small numbers. With reduction in the gram-positive organisms as the result of treatment, the gram-negative ones increased in numbers, and *H. influenzæ*, *E. coli* and members of the Neisseria group became predominant. In practically all the patients who showed this type of change in the nasopharyngeal flora, no complicating infections were seen. However, in 1 case, this type of change in bacterial flora resulted in pneumonia and bacteremia due to *H. influenzæ* and, in another, led to severe bronchitis and pneumonia due to *K. pneumoniæ*. These cases are described below.

**Case Reports.** CASE 1. A 4 year old white boy was admitted to the hospital because of pneumonia following measles. Six days previously, he had had a temperature of 104° F. and Koplik's spots. The next day, a typical morbilliform rash was present over the entire body. While the eruption was fading and the patient was apparently getting better, there was a sudden rise in temperature. A diagnosis of pneumonia was made and the child was sent to the hospital.

Physical examination on admission revealed an acutely ill boy who was breathing rapidly, with flaring of the alæ nasi, and had a non-productive cough. The temperature was 105.8° F., the pulse 160, the respirations 42, and the blood pressure 110/64. The skin showed a diffuse fading measles rash. The pharynx was slightly reddened but showed no other abnormalities. Examination of the lungs revealed widespread fine, crackling moist râles. The remainder of the physical examination was within normal limits.

The urine on admission was clear except for 1+ albumin. The hemoglobin was 10.6 gm. per 100 cc., and the white cell count 8300, with 62% neutrophils, 34% lymphocytes, 3% monocytes and 1% eosinophils. A blood culture was sterile. The nose and throat revealed a preponderance of nonhemolytic *Staph. aureus*, but alpha streptococci, diphtheroids, and *N. catarrhalis* were also present.

Penicillin in a dosage of 15,000 units every 3 hours was administered immediately after admission, and continued for

18 days. The temperature remained elevated to high levels during the first 2 days and there appeared to be some spread of the pneumonic process. The quantity of penicillin was increased, therefore, to 25,000 units every 3 hours. Following this, there seemed to be some improvement and the temperature fell to 101° F., but on the 5th hospital day suddenly rose to 104° F. The patient appeared considerably more ill, and the pneumonia seemed to have spread further. Although nose and throat cultures were made daily, *H. influenzæ*, Type B, was isolated in almost pure culture from these sources for the first time on the 4th day. It had not been detectable in the cultures made before this time. A blood culture taken on the 5th day revealed the influenza bacillus. The white cell count rose to 16,500, with 84% polymorphonuclear leukocytes, most of which were young forms. On the 5th day, the cold agglutinin titer of the blood was 1:64.

Because of the failure to respond to penicillin and the recovery of *H. influenzæ* from the throat and blood late in the course of the disease, it was thought that the patient had had an atypical viral bronchopneumonia which had become complicated by secondary infection with *H. influenzæ*. Therefore, 1 gm. of streptomycin per day was administered in divided doses every 3 hours intramuscularly, and penicillin was stopped. The temperature fell promptly to normal levels for 1 day and then rose again to 105° F., with an increase in the white blood cell count to 29,450. At this time, marked redness, swelling, heat and tenderness were noted in the lateral aspect of the right thigh at the site of a needle puncture for hypodermoclysis. Because of the presence of this subcutaneous infection, penicillin treatment was resumed. The 2 antibiotic agents were administered together and the temperature promptly returned to normal, where it remained for the remainder of the hospital stay. The area of inflammatory reaction in the leg gradually subsided, the changes in the lungs cleared, and the respiratory rate fell to normal. The patient was completely well when discharged from the hospital 27 days after admission.

Case 2. A 53 year old white man was admitted to the hospital with a diagnosis of faucial diphtheria. His illness had begun 1 week previously with a sore throat; this became rapidly and progressively worse until he was extremely weak, unable to swallow and had moderate dyspnea. No treatment was given except for 50,000 units of penicillin every 4 hours for 3 days prior to admission.

Physical examination revealed a well-developed, moderately obese man who appeared acutely ill and was breathing with some difficulty. The temperature was 102°, pulse 108, respirations 30, and blood pressure 110/80. The pharyngeal mucosa was covered by a thick grayish white exudate which extended onto the soft palate and over both tonsillar fossæ, and covered the entire uvula. The breath had a pungent, fetid odor. There was limitation of motion of the left side of the chest and dullness to percussion over the entire left lung anteriorly and posteriorly; the breath sounds were markedly diminished just below the scapula and were barely audible over the left base. No bronchial breathing was heard and only occasional coarse râles were audible. The lung findings were interpreted as due to extension of diphtheritic membrane down the trachea and into the left lung, since the patient was very hoarse. The trachea was in the midline. The heart was within normal limits except for a rate of 102. The remainder of the physical examination was not remarkable except for moderate cyanosis of the nail beds and lips.

The urine had a specific gravity of 1.022, and contained 80 to 100 white blood cells per high power field on admission but was within normal limits thereafter. The white blood cell count was 29,700, with 79% neutrophils, 18% lymphocytes, 2% monocytes and 1% basophils. A blood culture was negative. Culture of the nose and throat revealed large numbers of hemolytic *Staph. aureus*, *C. diphtheriæ* and Type 14 pneumococcus. *K. pneumoniæ* was not found in the nose or throat on admission.

The patient was given 100,000 units of diphtheria antitoxin immediately after admission, and started on a regimen of 30,000 units of penicillin every 3 hours intramuscularly. In the next few days, the temperature gradually returned to normal and improvement in the clinical status took place; during this time several pieces of tough diphtheritic membrane were coughed

up. On the 2nd hospital day, following a violent coughing spell, the patient developed interstitial emphysema, the air being present subcutaneously over the upper part of the chest, neck and face; this disappeared within 24 hours. On the 5th day, dyspnea became more marked and there were signs of fluid in the left chest. Thoracentesis yielded 600 cc. of sterile serosanguineous fluid which contained 15,000 erythrocytes and 750 leukocytes, 42% of which were neutrophils, 39% lymphocytes and 19% epithelial cells. The total protein was 3.62 gm. per 100 cc. and the fluid clotted on standing. One day prior to chest tap (4th day), the patient began to cough up thick, purulent, blood-streaked sputum which contained large numbers of *K. pneumoniæ* and *E. coli*. None of the throat cultures which had been done previously (daily) had ever revealed any gram-negative organisms. Bacteriologic examinations of the throat and sputum subsequent to the 4th day showed only *E. coli* and the Friedländer's bacillus. Many fine and coarse moist râles were present in both lungs continually from the 4th day, and cough and expectoration of bloody, purulent sputum increased. On the 6th day, the patient began to have more difficulty in breathing, gradually went into peripheral vascular collapse, and in spite of intensive therapy, including 0.5 gm. of streptomycin given intramuscularly every 3 hours, expired early on the 7th hospital day.

Electrocardiograms taken revealed no abnormalities on the day of admission, auricular premature systoles in all leads on the 4th day, and right bundle branch as well as complete heart block on the day preceding death.

*Postmortem examination* showed a diffuse myocarditis which grossly resembled that of diphtheria. The mucosa of the entire tracheobronchial tree was markedly reddened and there was a small amount of purulent exudate in the bronchi. The lungs were the seat of an early bronchopneumonia. Culture of numerous areas in the pulmonary tissues revealed only *K. pneumoniæ*. Two blood cultures taken on the day of death were sterile.

Case 3. A 3 year old girl was admitted to the hospital because of fever and abdominal pain. Two and a half years prior to admission she had had a "kidney infection," from which she recovered in 23 days. Seven weeks before coming to the hospital she had uncomplicated pertussis. Six hours before admission, there was a sudden onset of abdominal pain and vomiting. The temperature was elevated to 101.2° and the patient was brought to the hospital.

On admission the temperature was 99° F., the pulse 160 and the respirations 26. Physical examination was entirely within normal limits except for slight distention of the abdomen and generalized abdominal tenderness, somewhat more marked on the right. Peristaltic sounds were diminished. No tenderness could be detected in the costovertebral angles. The white cell count was 24,100, with 84% neutrophils and 16% lymphocytes. Examination of the urine revealed a specific gravity of 1.020, 2+ albumin, and 50 to 60 white cells per high power field, in a catheterized specimen. The hemoglobin was 11 gm. per 100 cc. Culture of the urine revealed *H. influenzæ*, which was neither Type A or B.

Streptomycin, 125 mg. every 3 hours, was administered intramuscularly for 5 days. The temperature remained normal during the entire course of treatment, and the urine was sterile 24 hours after beginning therapy with the antibiotic agent. The leukocytes in the urine decreased rapidly until, on the 5th day, there were only 1 or 2 per high power field; the albuminuria disappeared. The white cell count fell to 9100 by the end of 10 days. The temperature throughout the hospital stay was normal except for the 6th and 19th days, when it rose to 100.4° and 100.8°, respectively. On the 7th day, the number of white cells in the urine increased to 30 to 40 per high power field. Thereafter, pyuria persisted, with 12 to 20 white cells per high power field in catheterized specimens. Simultaneously with the recurrence of pyuria, non-hemolytic *Staph. aureus* was cultured from the urine; this organism was isolated a number of times during the remainder of the hospital stay.

Because of the recurrent pyelonephritis, the patient was referred to another hospital for complete study of the renal tract.

Case 4. A 10 month old girl was referred to the hospital because of drowsiness of 2 days duration and vomiting and fever (103° F.) and stiffness of the neck for 24 hours.

The striking findings on physical examination at admission were extreme restlessness, tachypnea, bilateral internal strabismus, stiffness of the neck and back, and positive Kernig's sign. The temperature was 105.6° F., the pulse rate 150 and respiration 44 per minute. The urine was within normal limits. The white cell count was 10,850, with 70% neutrophils, 29% lymphocytes and 1% monocytes. The spinal fluid was under increased pressure and contained 18,250 cells, 80% of which were neutrophils; the protein was 114 mg. per 100 cc., and the sugar 26 mg. *H. influenzæ*, Type B, was present in both the spinal fluid and blood. Cultures of the nose and throat revealed diphtheroids, alpha streptococci, and few colonies of *Staph. aureus* and *N. catarrhalis*.

Immediately after admission, treatment with streptomycin, 0.1 gm. every 3 hours intramuscularly, was started and continued for 5½ days. It was then omitted for 2 days following which 1.2 gm. was administered in the next 30 hours. Fifty mg. of the antibiotic agent were instilled into the spinal canal on admission, and 0.025 gm. given every 24 hours thereafter for the next 10 days. The blood and spinal fluid were cleared of *H. influenzæ* 24 hours after treatment was started and remained sterile for the rest of the hospital stay.

There was moderate improvement in the clinical condition, and the temperature returned to normal on the 5th day, but coma and twitchings persisted. Bacteriologic examination of the nose and throat revealed that on the 5th day and every day thereafter, a pure culture of hemolytic *Staph. aureus* was present. The temperature rose to 102° F. on the 8th day and remained at high levels for the rest of the course. On the 9th day, moist cracking râles were heard throughout both lung fields, and Roentgen ray examination revealed diffuse bilateral bronchopneumonia. Penicillin, 120,000 units per day, was given intramuscularly for 3½ days but the coma persisted, convulsions became more frequent and severe, and death occurred on the 12th hospital day. Cultures of the blood during the last 2 days of life revealed hemolytic *Staph. aureus*.

At autopsy the brain was essentially normal except for 2 small plaques of fibrin, 1 on each of the cerebral hemispheres, from which no bacteria were recovered. The lungs were the seat of a very diffuse, confluent bronchopneumonia from which coagulase-positive, hemolytic *Staph. aureus* was isolated.

Case 5. A 4 month old boy was sent to the hospital because of convulsions of 24 hours duration. The illness began about 10 days prior to admission, when after a mild upper respiratory infection, he suddenly developed a temperature of 103° F. Treatment with one of the sulfonamides produced a moderate degree of improvement, but on the day before entry the patient began to have frequent episodes of generalized convulsions. He was admitted to another hospital where lumbar puncture revealed a cloudy spinal fluid containing gram-negative pleomorphic bacteria and was therefore referred to the Haynes Memorial Hospital.

On admission to this hospital, the temperature was 102.2° F. and the respirations 32. The positive physical findings were marked generalized rigidity, bulging of the anterior fontanelle, slight reddening of the tympanic membrane on the right, a small amount of purulent exudate and reddening of the mucous membrane of the nose, marked stiffness of the neck and back, and positive Kernig's sign.

The urine was essentially normal. The white blood count was 8520, with 46% neutrophils, 49% lymphocytes, 3% monocytes and 2% basophils. The hemoglobin was 11 gm. per 100 cc. Lumbar puncture revealed an initial pressure of 280 and the spinal fluid contained 36,400 cells, 91% of which were polymorphonuclear leukocytes; the sugar was 30 mg. per 100 cc., and the protein 50 mg. Direct examination and culture of the spinal fluid revealed *H. influenzæ*, Type B. Bacteriologic examination of the blood and nose yielded the same organism. Throat culture revealed *N. catarrhalis*, diphtheroids, alpha streptococcus and a few colonies of *Staph. aureus*.

The patient was given 0.05 gm. of streptomycin every 3 hours intramuscularly, and 0.02 gm. of the drug was administered intrathecally every 24 hours except for the 2nd, 3rd and 4th days, when it was given every 12 hours. Intramuscular therapy was continued for 8 days and intrathecal treatment for 13 days. The causative organisms disappeared from the spinal

fluid and blood within 24 hours after streptomycin was exhibited, and the patient appeared to be making a rapid recovery. On the 7th day, there was a sudden elevation of temperature to 104.6° F., and the blood and spinal fluid were found to contain coagulase-positive hemolytic *Staph. aureus* every day from the 7th to the 14th day. *Staph. aureus* was present in pure culture in the nose and pharynx for the first time on the 5th day and daily thereafter until intensive penicillin therapy was administered. On the 10th day, a punctate erythematous rash resembling scarlet fever made its appearance; this increased in intensity for 48 hours and then began to fade, disappearing completely after 6 days. Because of the persistence of *Staph. aureus* in the spinal fluid and blood, penicillin was given in doses of 25,000 units every 24 hours intrathecally and 15,000 units every 3 hours intramuscularly. Because this treatment did not produce clearing of the blood stream in 6 days, the amount of antibiotic agent given by both routes was doubled. Thereafter, the organisms decreased markedly in numbers in the throat and disappeared rapidly from the spinal fluid and blood. The patient made an uneventful recovery.

**Discussion.** Five cases have been described in which, during the course of specific antibiotic therapy, there developed new infections due to organisms that were not susceptible to the agent with which the primary disease was treated. In 1 patient who probably had atypical viral pneumonia, the administration of penicillin resulted in an overgrowth of *H. influenzæ* in the pharynx, followed by an invasion of the blood and respiratory tract. In another individual, treatment of faucial diphtheria was complicated by the occurrence of pneumonia due to the Friedländer bacillus. The other 3 cases were treated with streptomycin for *H. influenzæ* infections, and 1 developed bronchopneumonia with bacteremia, another meningitis with bacteremia, and a third recurrent pyelonephritis, all due to hemolytic *S. aureus*.

The mechanism by which this type of infection occurs is not completely clear. However, in 4 of the patients there was a remarkable change in the bacterial flora in the nose and throat before new infection developed. Organisms that were apparently present in such small numbers that they were not detected early in the course of the disease increased in number after treatment with penicillin or streptomycin and invaded the tissues. That the new infections were not merely the result of numerical increase of one of the normal inhabitants of the nose and throat is evidenced by the fact that changes in the nasopharyngeal flora following the use of either antibiotic substance were frequently observed without a resultant new infection. It is possible that in some persons, a high degree of bacterial antagonism exists in areas like the nasopharynx and that certain groups of bacteria are kept in check by others. So long as this normal relationship is not disturbed, the numbers and invasive ability of some of the organisms may be kept below a critical level; when, however, some of the bacteria are removed as a result of contact with an antibiotic agent of high specificity, those organisms that are unaffected by the drug increase sharply in number and possibly in virulence. This phenomenon may be entirely due to an increase in numbers of bacteria if the microörganisms are of sufficiently high virulence. These new infections were seen mainly in young children and in 1 middle-aged adult who had had a serious infection and intoxication for 1 week before antibiotic therapy was started. Age, therefore, may be a determinant factor. Other factors that tend to produce lowered resistance, such as chronic debilitating disease, senility, etc., may also be of importance.

The type of organisms normally present in the pharynx is dependent to some degree on the general distribution of various bacteria in the population during certain seasons of the year. This will determine, in part, the organism that produces a new infection during the course of antibiotic therapy; for example, in the summer season the carrier rate for *H. influenzæ*

is low and the chance that invasion by this organism will occur as a result of penicillin treatment is less than it is in the winter. *Staph. aureus* is present in the pharynx of most persons at all times, so that the seasonal factor probably plays only a minor rôle in production of disease by this organism in patients who receive streptomycin.

The spontaneous occurrence of new infections due to non-susceptible organisms during the course of penicillin or streptomycin therapy raises the question of the use of either of these drugs in instances where the exact bacteriologic diagnosis is unknown, because patients may be exposed to the added danger of superimposed bacterial disease without any benefit to the primary process. For example, the treatment of virus infections with either streptomycin or penicillin may be dangerous because these drugs have no effect on the primary disease, and may allow organisms that are normally present on various tissues and are not susceptible to their activity to grow profusely and invade. The occurrence of this type of secondary infection is a strong argument for limiting the use of the antibiotic agents to those cases in which bacterial disease is proven by isolation of the causative agent or to those in which the possibility of bacterial infection is very strong.

Although it might appear that the availability of such agents as streptomycin and penicillin has reduced the necessity for careful bacteriologic studies in patients with infectious diseases, the exact opposite is the case. The highly specific antibacterial activity of these drugs necessitates exact identification of the causative agents of the infections for which they are used, and the need for careful bacteriologic study is greater now than it was prior to the advent of the antibiotic substances. This applies not only to the period of the disease before treatment is started but also to the time during which therapy is being given, lest the manifestations of new infections of the type described in the cases reported above be misinterpreted as due to failure of the original disease to respond to the drug being used. Frequent bacteriologic examination of the blood and of the nose and throat of patients who are being treated with an antibiotic agent, even though they seem to be progressing well, is to be highly recommended because a marked increase in numbers of an organism in the nasopharynx frequently precedes its invasion of the tissues by at least 24 hours. The discovery of a preponderance of *H. influenzæ* or *S. aureus* in the nasopharyngeal flora during the course of penicillin or streptomycin treatment should put the physician on guard for a complicating infection due to either of these organisms, particularly if the patient is a young child.

Since new infections may occur spontaneously during the administration of penicillin or streptomycin, the question may be raised whether or not these 2 agents should be given simultaneously to patients who are particularly susceptible to such an event, namely the very young or very old, or those with chronic debilitating disease. The combined use of the antibiotic drugs in a shotgun fashion with the implication that bacteriologic examination is then not necessary can only be decried. Although each of these agents is, on the whole, non-toxic, certain patients may become sensitized to them to the point where they cannot be used. Treatment with a combination of both drugs with an untoward sensitizing reaction may preclude the use of either agent some time later in the patient's life when his survival may depend on them. To advocate the employment of a combination of penicillin and streptomycin would result in even greater misuse of these drugs than they are at present subjected to, and would only further their use in many diseases in which there is no infectious basis.

**Conclusions.** 1. Five cases of complicating infections occurring during the course of treatment with antibiotic agents,

2 following penicillin therapy and the others following streptomycin treatment, have been described. In all of these the second infection was produced by organisms normally present in the nasopharynx and was not the result of the accidental introduction of bacteria.

2. The development of spontaneously occurring new infections during the course of penicillin or streptomycin therapy is a constant danger and must be watched for with great care.

3. The need for intensive bacteriologic study before and during the treatment with antibiotic agents cannot be overemphasized.

4. The use of streptomycin and penicillin simultaneously at the beginning of treatment of an infectious disease is not recommended.

Cases 4 and 5 have previously been reported in greater detail in the New England Journal of Medicine.[2]

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# INEFFECTIVE USE OF STREPTOMYCIN IN RHEUMATOID ARTHRITIS

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An infectious polyarthritis of rats, first described by Collier,[1] appears to be identical with or closely related to the rat disease shown by Findlay, Mackenzie, MacCallum and Klieneberger[3] to be due to a pleuropneumonia-like organism. Sabin[8] described a proliferative polyarthritis of mice produced experimentally with a pleuropneumonia-like organism, and Preston[7] isolated a similar organism from spontaneous rat arthritis and was able to reproduce the disease in rats. The possibility that this polyarthritis of rats and mice might be a counterpart of human rheumatism stimulated studies[11] which at first indicated that pathogenic pleuropneumonia-like organisms could be obtained from exudates and tissues of patients with rheumatic fever. However, in further investigations this was disproved.[7,12]

In spite of such negative findings there remained the fact that Findlay, Mackenzie and MacCallum,[4] and, later, Sabin and Warren[9] found that certain gold compounds exert a curative effect on arthritis of rats and mice due to pleuropneumonia-like organisms. Since gold salts also appear to have a beneficial effect in human rheumatoid arthritis, it seemed possible that the experimentally produced disease of rodents might serve to screen compounds for possible effectiveness in rheumatoid arthritis.

A pleuropneumonia-like organism was isolated in this laboratory from a spontaneous joint infection in a laboratory rat. This animal showed a swollen right foreleg, particularly at the radiocarpal joint, and the initial culture was obtained by aspirating a drop of fluid from the joint and culturing in beef infusion broth enriched with 30% ascitic fluid. On incubation at 37° C. for 24 hours, this and subsequent cultures in the same medium showed marked turbidity, and after an additional 24 hours incubation the growth generally settled as a deposit of flakes in the bottom of the tube. Microscopically the culture showed either small gram-negative bacilli or gram-negative débris or both. Electron micrographs of the organism were presented from these laboratories by Weiss.[13]

The technique for reproducing arthritis in normal rats consisted in injecting 0.5 cc. of 24 hour ascitic fluid broth culture intravenously. During the 3rd, 4th and 5th days after injection, a progressive polyarthritis developed, in which there were fusiform swellings of the toes, and progressive swelling of leg joints, the skin over these areas becoming tight and glistening and red or purplish in color. Within a few days, many of the infected rats showed a hemorrhagic deposit and edema about the nose and sometimes a conjunctivitis. An occasional rat had neurologic symptoms. Animals infected as described and receiving no chemotherapy died, generally in about 2 or 3 weeks. Treatment with gold sodium thiomaleate (myochrysine) was quite generally effective as noted in an earlier publication.[5]

During the past 2 years, using myochrysine-treated rats as a standard for comparison, we have examined more than 65 compounds as to their effect against this type of arthritis. Among these was penicillin[6] which, like all the others, failed to compare at all favorably with the gold salt. However, when streptomycin was used a result superior to that obtained with the myochrysine was consistently observed.[6]

In the first experiment, 4 infected rats of about 100 gm. weight were treated with

streptomycin hypodermically, while 6 animals were retained as controls. Therapy was started about 1 hour following infection, and 3 doses of 1 mg. each were given 1st, 2nd and 3rd days, for a total of 9 doses. The 4 treated rats remained entirely free of symptoms, while 5 of the 6 controls developed pleuropneumonia infection. Two of these were dead in 5 days, before definite gross arthritis could appear, but the other 3 developed disabling joint involvement.

As recounted elsewhere,[6] this experiment was repeated with larger groups of animals and with almost identical results.

Clinical Use of Streptomycin. The finding of a chemotherapeutic agent which appeared superior to gold salts in treatment of rat polyarthritis prompted experimental use of streptomycin in human rheumatoid arthritis. Sufficient drug was obtained for treatment of 5 patients through the offices of C. S. Keefer, M.D., Chairman of the Committee on Chemotherapeutic and Other Agents, National Research Council. Subsequently, treatment of 4 patients with higher dosage was attempted in order to reach a definite and final conclusion.

Patients were selected to represent both early and advanced types of rheumatoid arthritis but in each instance unmistakably active disease was present as indicated by the criteria established by a committee of the American Rheumatism Association.[2] The duration of disease from the initial attack of arthritis ranged from 7 months up to as long as 10 years, but in only 1 patient (E. W.) had there been almost continuous arthritis for a prolonged period of time. In the others the disease had been more or less intermittent, the current attacks being, with 2 exceptions, no longer than 12 months. The systemic symptoms of rheumatoid arthritis were present in all, and each patient had an elevated erythrocyte sedimentation rate. Ages ranged from 24 to 52 years, and there were 8 females and 1 male.

The disease activity was graded as either 2+ or 3+ in all instances on a scale in which 1+ indicates minor but definite evidence of rheumatoid arthritis and 4+ the fulminating type of disease.

Roentgenographic evidence of disease in the involved joints varied from minor bone atrophy without other findings in the earliest case to narrowed joint spaces and evidence of destruction of articular surfaces in the most advanced case. Except for the elevation in sedimentation rate, laboratory examinations indicated only the commonly found secondary anemia so often seen in rheumatoid patients.

Dosage. The first 5 patients were given 10 gm. of streptomycin in either 5 or 6 days with single doses of 200 or 250 mg. injected intramuscularly at intervals of 3 hours. Blood concentrations of streptomycin were calculated for 2 of these patients with the paper disk-plate method using *Staph. aureus* as the test organism.[10] In 1 case, concentrations of 0.019, 0.012 and 0.004 mg. per cc. were obtained at the end of 1, 2 and 3 hours following a dose of 200 mg., while the other patient showed ascending concentrations following injection of the same amount, the readings being 0.012, 0.016 and 0.019 mg. per cc.

To complete the study it seemed desirable to treat other patients with large doses on the order of 4 gm. daily for 20 days. Only 1 of those selected was able to complete such a course. Two others developed toxic symptoms, later described, which limited their high dosage treatment to 6 days for a total of 25 gm. in 1 instance, and 7 days and 29 gm. in the other. After discontinuance of therapy and disappearance of toxic symptoms these patients were given an additional 2 gm. each, only to have evidence of intolerance return. The fourth patient was given the balance of streptomycin remaining on hand at the rate of 4 gm. daily for a total of 30.5 gm. The maximum blood concentration of streptomycin obtained in estimations on 2 patients was 0.231 mg. per cc. 1 hour after injection of 500 mg.

Results of Treatment. Careful joint evaluations were done on each patient before and after treatment and again at

TABLE 1.—ANALYSIS OF DATA

| Case | Age | Sex | Duration since first attack | Duration of current attack | Degree of disease activity | Streptomycin (intramuscular) | | | | Clinical results | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Daily dose (gm.) | Total dose (gm.) | Max. blood conc. (mg. per cc.) | Side effects | Immediate | | Sedimentation (mm. hr. Wintrobe) | | Follow-up result |
| | | | | | | | | | | Objective | Subjective | Before | After | |
| O. S. | 24 | F | 4 yrs. | 12 mos. | 2+ | 1.6 (200 mg. q. 3 hrs.) | 10 (in 6 days) | 0.019 | None | Not impr. | Mod. impr. | 14 | 25 | Severe joint pain in 1 wk. |
| I. J. | 38 | F | 7 mos. | 7 mos. | 2+ | 1.6 (200 mg. q. 3 hrs.) | 10 (in 6 days) | 0.019 | None | Not impr. | Mod. impr. | 15 | 19 | Joint pain 3 days after discharge |
| L. M. | 37 | F | 10 yrs. | 3 yrs. | 3+ | 2.0 (250 mg. q. 3 hrs.) | 10 (in 5 days) | 0.010 | None | Not impr. | Mod. impr. | 21 | 15 | Subjective impr. for 4 mos. |
| V. B. | 36 | M | 7 yrs. | 12 mos. | 2+ | 1.6 (200 mg. q. 3 hrs.) | 10 (in 6 days) | 0.013 | None | Not impr. | Mod. impr. | 39 | 44 | Subjective impr. for 5 mos. |
| H. G. | 25 | F | 2 yrs. | 2 yrs. | 2+ | 2.0 (250 mg. q. 3 hrs.) | 10 (in 5 days) | .. | Dizziness | Not impr. | Mod. impr. | 28 | 32 | Subjective impr. for 4 mos. |
| E. W. | 40 | F | 6 yrs. | 6 yrs. | 2+ | 4.0 (500 mg. q. 3 hrs.) | 80 (in 20 days) | 0.231 | Hyperpyrexia; nausea | Not impr. | Sl. impr. | 38 | 32 | Acute joints continued unchanged |
| F. M. | 52 | F | 18 mos. | 18 mos. | 2+ | 4.0 (500 mg. q. 3 hrs.) | 25 (in 6 days) | .. | Hyperpyrexia; nausea; generalized skin eruption: purpura | Not impr. | Mod. impr. | 33 | 35 | Sl. impr. for 2 mos. |
| | | | | | | 2.0 (250 mg. q. 2 hrs.) | 2 (in 1 day) | | | | | | | |
| L. O. | 49 | F | 27 mos. | 3 mos. | 2+ | 4.0 (500 mg. q. 3 hrs.) | 29 (in 7 days) | .. 0.042 | Hyperpyrexia; nausea; generalized skin eruption | Not impr. | Sl. impr. | 32 | 36 | Acute joints continued unchanged |
| | | | | | | 2.0 (500 mg. q. 3 hrs.) | 2 (in 4 doses) | | | | | | | |
| B. J. | 51 | F | 9 yrs. | 3 mos. | 3+ | 4.0 (500 mg. q. 3 hrs.) | 30.5 (in 8 days) | .. | Nausea; deafness; vertigo | Not impr. | Sl. impr. | 30 | 35 | Acute joints continued unchanged |

longer intervals during the follow-up period. Notations were made without reference to earlier examinations in an effort to record unbiased opinion. In no case was there definite evidence of objective improvement. As is so often true with new remedies for arthritis, subjective improvement was quite general, and 3 patients elaimed definite benefit for as long as 4 or 5 months following completion of treatment. It is interesting to note that those receiving the greatest amount of streptomycin seemed to improve the least. The erythrocyte sedimentation rate was not altered significantly by streptomycin.

Toxic Effects. Among the 5 patients given a daily dose of 1.6 or 2 gm. only 1 complained of what may have been evidence of intolerance to streptomycin. After isolated doses there was a transient dizziness which was brief in duration and appeared to be of little significance. However, side-effects were quite general among those given 4 gm. daily. Nausea was a complaint of all 4, and it was of such intensity as to interfere with food intake. Three patients developed hyperpyrexia with temperatures occasionally rising as high as 104° F., but usually ranging from normal to 102° F. In each instance, temperatures leveled off to normal when streptomycin was discontinued. One patient (E. W.) continued with daily fever to 102° F. throughout 20 days of treatment.

Two patients developed a generalized skin eruption at the end of 6 and 7 days of high dosage therapy, 1 having had a total of 25 gm. and the other 29 gm. A macular rash first appeared over the chest and progressed to cover the entire body as a maculopapular eruption. In 1 of these cases purpuric spots appeared on the second day of the eruption. Streptomycin was stopped in both patients as soon as the skin lesions appeared and within 7 days all evidence of intolerance had disappeared. To prove that streptomycin was the provocative agent, both patients were again given the drug for a total second course of 2 gm. In both cases the rash was reproduced but with less intensity than on the first occasion.

One patient complained of deafness on the 7th day of treatment with 4 gm. daily. Streptomycin was stopped on the 8th day, at which time vertigo also was a complaint. There was prompt though incomplete recovery of hearing but the vertigo has persisted for 10 weeks at the time of writing this report.

**Summary and Conclusions.** 1. Polyarthritis of rats due to the pleuropneumonia-like organism isolated in these laboratories is not useful in screening drugs for possible effectiveness in human rheumatoid arthritis.

2. Effective treatment of this type of rat polyarthritis with streptomycin led to experimental use of the drug in 9 patients with rheumatoid arthritis. Total doses of 10 gm. given over a period of 5 or 6 days and larger total quantities ranging from 25 to 80 gm. given at a rate of 4 gm. daily did not appreciably alter the course of rheumatoid arthrit's in the cases studied.

3. With daily doses of 4 gm. of streptomycin, side-effects were quite general. These consisted of nausea, hyperpyrexia, skin eruption, and deafness with vertigo.

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# SULFATHIAZOLE IN THE ABNORMAL HUMAN BILIARY TRACT*

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Knowledge of the rôle chemotherapeutic agents play in diseases of the human gall bladder and bile ducts has been in a rather confused state. This prompted Zaslow, Counseller and Heilman[16,17] to study the problem with regard to the antibiotics, penicillin and streptomycin. These studies indicated that the agents were not excreted into the biliary tract in the presence of either mechanical obstruction of the bile duct, acute cholangitis or impaired hepatic function. It followed that these antibiotics were of little value under such circumstances in treating infections of the biliary tract. In addition, it also was observed that the antibiotics were not excreted through the wall of the gall bladder but reached the lumen through the bile flowing in the biliary tree. The uselessness of these drugs in treating local infection in the presence of acute obstructive cholecystitis was obvious. As a result of those studies, we decided to investigate the effectiveness of the sulfonamides. The present report deals with the excretion and concentration of sulfathiazole in the human gall bladder and bile ducts. A plan similar to that used in the previous investigation was followed.

**Review of Literature.** Carryer and Ivy[3] found high concentrations of sulfanilamide in dog's bile after oral administration of a single dose of 2 gm. Hubbard and Anderson[6] reported that sulfanilamide was regularly found in human bile drained from the bile ducts following oral ingestion of 2 gm. They also noted that a higher concentration of acetylated sulfanilamide appeared in the blood than in bile draining out of T tubes. Spink, Bergh and Jermsta[15] also reported that a greater concentration of the acetylated forms of sulfanilamide and sulfapyridine was found in the blood of man than in the bile and observed that the liver concentrated sulfapyridine but not sulfanilamide. Bettman and Spier[2] found that the degree of concentration of sulfanilamide in the human gall bladder was directly influenced by the concentrating power of that organ as measured by the Graham-Cole test. More recently Shay and co-workers[14] reported that following oral administration of the drugs the concentration of sulfathiazole and sulfasuxidine in dog's bile was more than 2 times that in the blood, while the concentration of sulfaguanidine in the bile was the same as that in the blood. However, they observed that some of these sulfonamides were not excreted into the dog's gall bladder and raised the question of their usefulness in treating disease of the gall bladder in which the cystic duct is occluded. Lynn, Bergh and Spink[8] had previously arrived at a similar conclusion regarding the action of sulfanilamide, sulfathiazole and sulfadiazine in the dog.

The evidence as to the clinical usefulness of these agents, although infrequent, is rather confusing. Cleveland,[5] reporting a case in which he believed that sulfanilamide was instrumental in curing cholangitis following choledochoduodenostomy, stated that the drug was indicated in treatment of damage to the liver associated with cholangitis. Mancke, Plötner and Siede[9] reported that they successfully treated 6 patients who had acute cholangitis by the use of prontosil either orally

* Estimations of sulfathiazole in bile were made in the Division of Biochemistry under the supervision of Dr. M. H. Power.

or parenterally administered. The dose was small, only 0.6 gm., 3 times a day. They noted, however, that there was no improvement in cases of chronic cholangitis. Rehfuss[13] stated that sulfonamides should be used in treatment of acute hepatitis and acute disease of the biliary tract, with the reservation that "when there is severe damage or mechanical obstruction, we can only hope to control temporarily the infection of the ducts in this way." Morrison reported that he was able to sterilize the biliary tracts of all patients who had streptococcal infection, but he did not name the associated condition in the biliary tree;[11] however, at a later date he added "provided there was no cystic duct obstruction in the dog or human."[10] He was unable to cure patients who were infected with *Escherichia coli*. Bazin[1] reported the case of a carrier of *Salmonella paratyphi* in which treatment with sulfanilamide was successful.

Contrary to the foregoing favorable reports, Spink, Bergh and Jermsta[15] could find no effect from sulfanilamide or sulfapyridine in the treatment of 2 patients whose bile ducts were infected with *E. coli*. Peterson, Deutsch and Finland,[12] although reporting favorably on the effect of sulfathiazole and sulfadiazine in treatment of acute hepatitis, noted only failure in 3 cases of cholangitis. Lembcke[7] reported failure in treating a typhoid carrier.

In general, when the sulfonamides were used in the treatment of infections of the biliary tract, any clinical improvement observed was attributed to the chemotherapeutic agents. Most often the occurrence of natural remission in the disease was disregarded. It appears that the usual assumption was that since the drugs were excreted in the bile of the normal dog and man, they were very likely also excreted into the obstructed and infected biliary tree.

The present investigation is reported in 2 parts: (1) sulfathiazole in the gall bladder; (2) sulfathiazole in hepatic bile.

1. Sulfathiazole in the Gall Bladder. *Method of Study.* Twenty-five patients scheduled for cholecystectomy were selected. At a definite interval before operation each patient was given 3 gm. of sulfathiazole orally. This was taken after fasting and no food was eaten after the drug was administered. The time elapsing between ingestion of the drug and performance of cholecystectomy was noted. The level of sulfathiazole in the bile removed from the gall bladder was determined by the method described by Carryer and Osterberg.[4] Only the level of free sulfathiazole was determined. Notes were made as to the presence and position of stones in the gall bladder at the time of operation. The condition of the liver and biliary tree, as well as the function of the gall bladder as determined by the Graham-Cole test, were recorded.

**Results.** (Table 1.) Seven patients had non-functioning gall bladders which contained stones. The time intervals between ingestion of sulfathiazole and determination of its concentration in gall bladder bile varied from $2\frac{1}{2}$ to 12 hours. In 4 cases no drug was found in the contents of the gall bladder; the cystic duct was obstructed by a stone in each case, 2 gall bladders were reported as hydropic and 1 showed microscopic evidence of acute inflammatory changes in the wall. The levels of sulfathiazole in the contents of the remaining 3 non-functioning gall bladders varied from 0.75 to 1.8 mg. per 100 cc.; the cystic ducts in these cases were patent.

There were 15 patients whose functioning gall bladders contained stones. The time elapsing from ingestion of sulfathiazole to determination of its concentration in gall bladder bile varied from 2 to 14 hours. In the gall bladder bile of 7 of these patients sulfathiazole was not found. In 6 of these 7 the cystic duct was obstructed by a stone at the time of operation; in the other patient, although the cystic duct was patent, drug was not found in bile from the gall bladder. This patient had marked obstructive jaundice; it is likely that no sulfathiazole was excreted by the liver. The findings in this case are explained in this report. The concentrations of drug in the bile of the remaining 8 patients who had functioning

gall bladders which contained stones varied from 0.31 to 2.7 mg. per 100 cc.

Three patients had no stones in the gall bladder at the time of operation. Sulfathiazole was not found in the bile of 1 patient who had obstructive jaundice at the time of operation; the concentrations of drug in the bile of the remaining 2 patients were 0.85 and 1.6 mg. per 100 cc., and the time intervals 5 hours and 3 hours, respectively.

Table 1.—Concentration of Sulfathiazole in Gall Bladder Bile Following Oral Administration of 3 Gm.

| Type of gall bladder | Concentration of free sulfathiazole (mg. per 100 cc.) | Time after ingestion (hrs.) | Obstruction cystic duct |
|---|---|---|---|
| Non-functioning (stones present) | 0.85 | 2½ | No |
| | 0 | 3 | Yes* |
| | 0 | 3 | Yes |
| | 1.80 | 4 | No |
| | 0 | 10 | Yes† |
| | 0 | 12 | Yes† |
| | 0.75 | 12 | No |
| Functioning (stones present) | 0.31 | 2 | No |
| | 0.94 | 2 | No |
| | 0 | 2½ | Yes |
| | 0 | 2½ | No‡ |
| | 0.70 | 2½ | No |
| | 0 | 3 | Yes* |
| | 0.45 | 3½ | No |
| | 1.88 | 5 | No |
| | 0 | 6 | Yes |
| | 0.85 | 4½ | No |
| | 0 | 10 | Yes |
| | 0 | 11 | Yes |
| | 0.71 | 12 | No |
| | 2.70 | 13 | No |
| | 0 | 14 | Yes |
| No stones | 1.60 | 3 | No |
| | 0.85 | 5 | No |
| | 0 | 14 | No‡ |

* Reported by pathologist as acute cholecystitis superimposed on chronic cholecystitis.
† Reported by pathologist as hydropic.
‡ Obstructive jaundice present.

**Comment.** It appears that the most important factors concerned with the appearance of sulfathiazole in the lumen of the gall bladder are the patency of the cystic duct and the ability of the liver to excrete the drug. In each case in which these factors were favorable the drug was recovered in bile from the gall bladder. While the concentrations were low, varying from 0.31 to 2.7 mg. per 100 cc. of bile, it must be remembered that only a single dose of 3 gm. was given orally. Had larger doses been given initially and repeated at definite intervals, it is likely that higher concentrations would have been attained. It cannot be stated with any degree of certainty either that the drug is absorbed from the lumen of the gall bladder or that it is greatly concentrated in the gall bladder. The fact that sulfathiazole was present as long as 13 hours after oral administration at least suggests that it can remain in a non-contracting gall bladder for long intervals. In addition, since in most instances the amount of sulfathiazole present was less than 1 mg. per 100 cc. of bile, it is likely that little concentration of the drug took place in the gall bladder.

It is also well to recall that in the 2 cases in which acute inflammation was found in the wall of the gall bladder no sulfathiazole was present in the lumen when the cystic duct was obstructed. This suggests that acute inflammation does not alter the mode of entrance of the drug.

2. SULFATHIAZOLE IN THE HEPATIC BILE. *Method of Study.* Ten patients who had undergone choledochostomy and insertion of a T tube were selected for study. Between the 4th and 7th days after operation each patient was given 3 gm. of sulfathiazole orally. This was given only in the absence of nausea and abdominal distention and when the patient was taking fluids well by mouth. Specimens of bile were collected from the T tubes at intervals of 2 to 6 or more hours. The concentration of sulfathiazole in the bile was determined by the method of Carryer and Osterberg. When jaundice was present, it was observed whether the jaundice was increasing or decreasing as indicated by the concentration of serum bilirubin. In most cases in which icterus was not present a sulfobromophthalein test for hepatic function was performed. In several cases in which 5 gm. of sulfathiazole were left in the abdominal cavity at operation, the concentration of sulfathiazole in the bile was determined 2, 4, 6 and 12 hours after operation. In a few cases all studies of excretion were repeated at intervals for 2 weeks after operation in order to determine whether there was any change in the ability of the liver to excrete the drug.

**Results.** (Table 2.) The cases were divided into 2 groups as determined by the ability or inability to excrete the drug as indicated by results of the initial tests.

*Group 1.* Five patients failed to excrete the drug at the time of initial study. A short résumé of the histories and pertinent laboratory studies is presented.

TABLE 2.—EXCRETION OF SULFATHIAZOLE IN HEPATIC BILE AFTER INGESTION OF 3 GM. OR INTRAPERITONEAL ADMINISTRATION OF 5 GM.

| Case | Jaundice (duration present attack, days) | Liver function test* (sulfobromophthalein) | | Preoperative serum bilirubin (mg. per 100 cc.) | | Excretion of sulfathiazole | |
|---|---|---|---|---|---|---|---|
| | | Grade | Postoperative day | Direct | Indirect | Mg. per 100 cc. (maximum)† | Postoperative day of test |
| 1 | 0 | 0 | Preop. | 0 | | 0 | 3 |
| | | 4 | 4 | 1.8 | 0.5 | 1.53‡ | 9 |
| | | 0 | 9 | 0 | | | |
| 2 | 0 | 1 | 4 | .. | .. | 0‡ | 4 |
| | | | | | | 1.29‡ | 8 |
| 3 | 2 | .. | .. | 11.0 | 0.7 | 0§ | |
| | | | | | | 0¶ | 5 |
| | | | | | | 0.60¶ | 14 |
| 4 | 1 | .. | .. | 9.0 | 2.7 | 0§ | |
| | | | | | | 1.72‡ | 14 |
| 5 | 7 | 2 | 3 | 3.5 | 0.5 | 0§ | |
| | | | | | | 0.19¶ | 6 |
| 6 | 0 | 2 | 6 | .. | .. | 0.18‡ | 5 |
| | | | | | | 0.34‡ | 7 |
| 7 | 3 | 0 | 14 | 6.3 | 2.1 | 0.44¶ | 3 |
| | | | | | | 1.50‡ | 15 |
| 8 | 0 | 3 | 5 | .. | .. | 0.42‡ | 3 |
| | | | | | | 1.22‡ | 9 |
| 9 | 0 | .. | .. | 0 | 0.8 | 1.55‡ | 4 |
| | | | | | | 1.55‡ | 10 |
| 10 | 0 | 4 | 5 | .. | .. | 1.76‡ | 4 |
| | | 0 | 7 | | | | |

* Grades 1 to 4 (1 is least) retention; Grade 0 is normal.
† Only the concentration of free drug was determined.
‡ Normal serum bilirubin concentration when test was made.
§ Intraperitoneal administration of drug.
¶ Serum bilirubin falling when test was made.

CASE 1. Several attacks of jaundice had occurred in preceding years, but none in the few months just before operation. All laboratory work, including a sulfobromophthalein test for hepatic function, gave negative results. At operation a gall bladder filled with stones was removed. The common duct was explored. While no stones were found, the bile was thick and inspissated. On the 3rd postoperative day

(day of operation is taken as the 1st) the patient failed to excrete sulfathiazole during a 6 hour period. A test for hepatic function performed on the 4th day showed retention of dye, Grade 4 (in which Grade 1 is least and Grade 4 most severe). The value for serum bilirubin at this time was 1.8 mg. per 100 cc. direct and 0.5 mg. indirect. The patient's course was uneventful; on the 9th postoperative day the patient excreted a maximum of 1.53 mg. of sulfathiazole per 100 cc. of bile and a test for hepatic function gave negative results.

We had expected this patient to excrete both test dye and sulfathiazole on the 4th and 3rd days, respectively; however, it appeared that either the operation or the anesthesia (nitrous oxide, oxygen, ether) or both had temporarily further impaired a liver which already had little reserve function as a result of previous icteric episodes. This impression is supported by the fact that the results of a test for hepatic function made before operation were negative, but results of a similar test performed on the 4th postoperative day indicated retention, Grade 4. The patient quickly recovered her ability to excrete both the test dye and sulfathiazole.

CASE 2. Repeated attacks of pain in the upper part of the abdomen, associated with jaundice and fever on a few occasions, had occurred in the 2 years before the patient's registration at the Mayo Clinic. All preoperative laboratory tests gave negative results. At abdominal exploration no abnormality was found in either the gall bladder or bile ducts. Cholecystostomy and choledochostomy were performed. It was thought that the patient probably had had recurrent attacks of intrahepatic jaundice. On the 4th postoperative day the patient failed to excrete in the bile any sulfathiazole in a 24 hour period. A test for hepatic function revealed retention of dye, Grade 1. The concentration of serum bilirubin was normal. The patient had a chill on the 5th postoperative day, her oral temperature rose to 102° F. and she complained of pain in the right upper quadrant of the abdomen similar to that experienced on previous occasions when she had been icteric. The symptoms rapidly subsided and no jaundice developed. On the 8th postoperative day another sulfathiazole test revealed that the patient excreted 1.29 mg. per 100 cc. of bile in a 2 hour specimen.

In Case 2, as in the preceding case, it appears that either the operation or the anesthesia or both had temporarily further impaired the function of a liver which already had little reserve.

CASE 3. Repeated attacks of biliary colic had occurred for many years. While undergoing study at the clinic, the patient had an attack of typical colic, followed by chills, oral temperature of 102° F. and jaundice. The value for serum bilirubin 2 days before operation was 11 mg. per 100 cc. direct and 0.7 mg. indirect. At operation the common bile duct was found to be greatly dilated; a stone was impacted in the lower end. Cholecystectomy, choledocholithotomy and choledochostomy were done. Five gm. of sulfathiazole were left in the abdominal cavity. Specimens of bile collected in a period of 6 hours contained none of the drug. On the 3rd postoperative day the value for serum bilirubin had decreased to 2.9 mg. per 100 cc. direct. The patient's general condition was satisfactory. On the 5th postoperative day, following oral administration of 3 gm. of sulfathiazole, no drug was found in the bile; however, when the test was repeated on the 14th day, a concentration of 0.6 mg. per 100 cc. was found.

This patient had active obstructive jaundice when the initial test was carried out. No sulfathiazole was excreted in bile at this time or on the 5th day. However, after most of the jaundice had disappeared, there was some excretion of the drug in the bile.

CASE 4. There was no previous history of disease of the gall bladder. However, on the day before operation the patient had an attack of pain in the right upper quadrant of the abdomen, followed by fever, jaundice and a rapidly developing perforation of the gall bladder. The concentration of serum bilirubin the day of operation was 9 mg. per 100 cc. direct and 2.7 mg. indirect. At operation bile was found free in the abdominal cavity. Cholecystectomy and choledochos-

tomy were done. No stone was found in the common duct at the time; it was thought inadvisable to explore too long because of the patient's poor condition. Five gm. of sulfathiazole were left in the abdominal cavity. There was no excretion of the drug in the bile in the first 10 hours after operation. The patient's condition steadily improved and the concentration of serum bilirubin gradually returned to normal. On the 14th postoperative day a concentration of 1.72 mg. of sulfathiazole per 100 cc. of bile was found after oral administration of the drug.

The same process as in Case 3 appears to have been active in Case 4.

CASE 5. Cholecystectomy and choledocholithotomy had been performed 1 year before the patient's admission at the clinic. Because of the large size of the duct and a persistent filling defect observed in the choledochogram, the T tube had been left in place for more than 3 months. The patient had been well following removal of the tube until a few days before readmission. At that time she experienced an attack of biliary colic followed by jaundice. The concentration of serum bilirubin 2 days before operation was 3.5 mg. per 100 cc. direct and 0.5 mg. indirect. At operation stones were not found in the common or hepatic ducts. The pancreas was normal. A T tube was left in the common duct. Three gm. of sulfathiazole had been given to the patient orally 1 hour before operation. None of the drug was excreted in the bile for 6 hours after operation. The postoperative course was uneventful. A test for hepatic function performed on the 3rd postoperative day revealed retention of dye, Grade 2. The concentration of serum bilirubin at that time was 1.1 mg. per 100 cc. direct and 0.9 mg. indirect. On the 6th postoperative day the patient excreted 0.19 mg. of sulfathiazole per 100 cc. of bile in a 3½ hour specimen obtained after the ingestion of 3 gm. of drug.

Case 5 seems to fall into the same category as Cases 3 and 4.

*Group 2.* Five patients excreted sulfathiazole in bile at the time initial tests were made.

CASE 6. Two attacks of jaundice had occurred, the most recent one a month previously. All preoperative studies gave negative results. At operation stones were not found in the common bile duct or gall bladder. The surgeon stated that hepatitis, Grade 2, was present. Cholecystectomy and choledochostomy were done. On the 3rd postoperative day the patient excreted 0.18 mg. of sulfathiazole per 100 cc. of bile in a 6 hour specimen obtained after oral administration of a dose of 3 gm. of drug. A test for hepatic function performed on the 5th postoperative day disclosed retention of dye, Grade 2. On the 7th postoperative day a concentration of 0.34 mg. of sulfathiazole per 100 cc. of bile was found on repetition of the test for excretion of drug.

Although this patient excreted sulfathiazole on both occasions, the value was low. This is compatible with the existence of the hepatitis found by the surgeon and with impairment of hepatic function as shown by results of the sulfobromophthalein test. It might very well have been that the previous attacks of jaundice were caused by hepatitis.

CASE 7. Attacks of colic in the right upper quadrant of the abdomen had occurred for 1 year. There had been no jaundice until several days before operation, when the patient had had an attack of colic followed by jaundice. The concentration of serum bilirubin the day before operation was 6.3 mg. per 100 cc. direct and 2.1 mg. indirect. At operation a carcinoma of the gall bladder which had invaded the liver was found. There were stones in the common duct and gall bladder. Cholecystectomy, partial hepatectomy, choledocholithotomy and choledochostomy were done. Following operation the value for serum bilirubin decreased to normal after the 1st week. Sulfathiazole was given orally on the 3rd postoperative day; as a result, 0.44 mg. of drug per 100 cc. of bile was found in a 6 hour specimen. The study was repeated on the 15th day. At that time a concentration of 1.5 mg. per 100 cc. was reached.

CASE 8.—Attacks of colic and jaundice had occurred 16 years and 1 year before admission at the clinic. There was no jaundice at the time of the present admis-

sion. At operation multiple stones were found both in the common bile duct and in the gall bladder. A test for excretion of sulfathiazole performed on the 3rd postoperative day showed a concentration of 0.42 mg. of drug per 100 cc. of bile in a 2 hour specimen. A test for hepatic function made on the 5th day disclosed retention of dye, Grade 3. A test for serum bilirubin gave negative results. On the 9th day administration of sulfathiazole resulted in the excretion of 1.22 mg. of drug per 100 cc. of bile in a 6 hour specimen. The results of a test for hepatic function were reported as negative at that time.

CASE 9. After cholecystectomy had been performed, many years before, the patient had had numerous attacks of colic, but no jaundice at any time. The preoperative concentration of serum bilirubin was normal. At operation many stones were found in the common duct. The duct was markedly dilated. A test for excretion of sulfathiazole made on the 4th day showed that 1.55 mg. of drug per 100 cc. of bile were excreted during a period of 6 hours. A similar test made on the 10th day gave similar results.

CASE 10. A history of jaundice and colic was elicited. At operation stones were not found in the common bile duct but many were found in the gall bladder. Cholecystectomy and choledochostomy were done. A test for excretion of sulfathiazole performed on the 5th postoperative day showed a value of 1.76 mg. of drug per 100 cc. of bile in a 4 hour specimen. A test for hepatic function made on the same day revealed retention of dye, Grade 4, but a similar test made 2 days later showed no retention.

**Comments.** Three of the 5 patients who excreted no sulfathiazole in bile when the initial study was made had obstructive jaundice which was either stationary or was not subsiding rapidly at the time of operation. When the jaundice started to subside after operation, sulfathiazole in greater or lesser amounts was found in the bile. Two patients who failed to excrete the drug did not have jaundice at the time of operation; however, the drug was excreted in large amounts 8 and 9 days later, respectively. It is suggested that the damage incidental to anesthesia and operative manipulation was probably sufficient in these 2 cases to impair hepatic function.

The remaining 5 patients excreted variable amounts of the drug, as indicated by the results of initial tests. Only 1 patient (Case 7) was icteric at the time of operation and the icterus appeared to be subsiding. One patient (Case 6) who was thought to have hepatitis, confirmed by the occurrence of retention of dye, Grade 2, as shown by tests made 3 and 7 days postoperatively, failed to excrete more than 0.34 mg. of drug per 100 cc. of bile. These concentrations were definitely low. Four patients (Cases 7, 8, 9 and 10) each secreted more than 1 mg. of sulfathiazole per 100 cc. of bile in either initial or subsequent tests. Two patients (Cases 9 and 10) who did not have jaundice and whose tests for hepatic function gave negative results excreted, respectively, 1.55 mg. of sulfathiazole per 100 cc. of bile and 1.76 mg. at the time of initial examination.

From this study it appears that either active obstruction of the bile ducts or hepatic damage may hinder or prevent excretion of sulfathiazole in bile. When either is marked, none of the drug is excreted. However, as obstruction is overcome and hepatic function returns, as it will if damage is not great, more and more of the drug is excreted by the liver.

**Clinical Importance.** It is apparent that the cystic duct must be patent for sulfathiazole to reach the lumen of the gall bladder. Morrison observed the importance of this factor in treating infections of the gall bladder in both the lower animal and man. The roentgenologic findings as to the function of the gall bladder cannot be relied on to reveal whether the duct is patent at the time treatment is given, since a gall bladder which contains stones may become obstructed at any time. It follows, then, that any chemotherapeutic approach to treatment of chronic disease of the gall bladder is at best uncertain. In treatment of acute obstructive cholecystitis we can state more definitely that

the drug most likely would be of no local value.

Since sulfathiazole is not excreted in the bile during active obstruction of the biliary ducts, it is difficult to see how this drug can be effective in the treatment of cholangitis associated with obstructive jaundice. We seriously question the good results attributed to the drug under such circumstances. Rather, it would seem that the infection subsides spontaneously. The drug likely may prove of value in preventing spread of infection to the parenchyma of the liver. For sulfathiazole to be effective, a free flow of bile must be established either by external or internal drainage and the liver must not be so seriously damaged that it cannot excrete the drug.

While this study was concerned only with the excretion of sulfathiazole, a few preliminary studies in which sulfanilamide and sulfadiazine were used have shown similar results.

**Summary and Conclusions.** Concerning Sulfathiazole in the Gall Bladder. 1. Following oral administration of 3 gm. of sulfathiazole:

(*a*) No drug was found in bile from the gall bladder when the cystic duct was obstructed.

(*b*) The drug was present in bile from the gall bladder when the cystic duct was patent and when the liver excreted it normally.

2. Sulfathiazole is likely to be of no value in the treatment of patients who have acute obstructive cholecystitis.

3. The usefulness of sulfathiazole in treatment of any given patient who has chronic cholecystitis with stones is uncertain.

4. Acute inflammation of the gall bladder does not alter the mode of entrance of the drug to its lumen.

Concerning Sulfathiazole in Hepatic Bile. 1. After oral ingestion of 3 gm. of sulfathiazole or intraperitoneal administration of 5 gm., the drug is excreted in the hepatic bile of normal patients.

2. In the presence of obstructive jaundice the ability of the liver to excrete the drug is impaired.

3. The greater the degree of hepatic damage the less is the amount of drug excreted in the bile.

4. As the concentration of serum bilirubin approaches normal, more sulfathiazole is excreted in bile.

5. Sulfathiazole is likely to prove of no value in treatment of patients who have acute obstructive jaundice with cholangitis.

6. Free drainage of bile must be established if the drug is to be active.

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# REITER'S SYNDROME

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Renewed interest has recently been stimulated in the study of Reiter's syndrome, a disease entity of unknown etiology whose classical manifestations are the triad of urethritis, arthritis and conjunctivitis. Since Reiter's original descriptive communication in 1916, less than 80 additional cases in 29 articles have been reported. These have appeared mainly in recent years from medical staffs of military installations where there were accumulations of large groups of young men whose age is apparently propitious to the disease.

Although the paucity of literature and general incognizance of the condition suggest the rarity of the syndrome, the observation of 12 cases in 2 years by a single observer refutes this contention and indicates the necessity for further awareness of the disease in diagnostic considerations. The propensity for exaggerated symptoms involving in 1 case 1 bodily system and in another a second, often simulating a diversity of other diseases, has obscured the diagnosis. Yet, since clinical inaccuracies engender misleading implications of therapy and prognosis, prompt recognition is important.

Historical. Attention was first called to the singular character of the disease by Reiter[10] in Germany during the first World War. He observed a soldier who, initially complaining of diarrhea, subsequently developed polyarthritis, purulent urethritis, conjunctivitis, mild cystitis and pustular lesions over the hips. Unable to ascribe specific cause to the complex and procuring no therapeutic success with the agents available to him, Reiter conceived of the syndrome as a new entity. Shortly thereafter 2 independent reports were made by Fiessinger[5] in France, and Macfie[9] in Africa.

Although sporadic reference to this curious disease continued in the foreign literature, the first American description appeared in 1942, when Bauer and Engleman[1] reported a series of 6 cases. In 1944, Lever and Crawford[8] contributed 2 more cases emphasizing the dire dermatologic complications that may result. Rosenblum[11] in 1945 reviewed 10 cases observed by him in a Naval Hospital. At the same time Hollander[7] and a group of investigators at an Army Medical Center reported a series of cases presenting a type of arthritis which they believed to be specific only for Reiter's syndrome. Colby,[3] and Sargent,[12] in separate publications, have more recently revealed the severity of complications involving the urinary tract. It is doubtful, however, whether in all these cases the patients actually had Reiter's disease, since in some the triad was not complete and in others the bacteriologic studies were not sufficient to exclude the possibility of a gonococcic infection.

The 12 cases selected in this series were those in which indisputable diagnosis could be made. In every instance the requisite specifications of the triad were met and meticulous clinical and laboratory study was performed to exclude all other clinical possibilities. So-called atypical cases are not recorded.

Clinical Picture in 12 Cases. The 12 patients observed were males between the ages of 19 and 34. All reported the illness as the initial episode and such follow-up studies as have been possible fail to disclose recurrence. Only 1 patient gave a family history of joint disease. Previous episodes of gonorrhea were established in 6 cases, only 1 of which, however, preceded the onset of Reiter's disease by less than 6 months. History

of non-specific urethritis was recorded by 2 patients; in both instances no complications had ensued and symptoms had subsided promptly. In 1 case recurrent attacks of conjunctivitis without other manifestations were noted for 2 years prior to the syndrome.

The initial symptom in 9 cases was urethritis. Conjunctivitis occurred simultaneously with urethral discharge in 1 patient and mild diarrhea heralded the onset of disease in another. In only 1 instance did the arthritis appear in precedence to the other signs. The time required for the complete syndrome to develop varied from 2 to 30 days; usually the clinical picture was complete within the first 10 days of illness.

The urethral discharge usually began as a glairy mucoid exudate which later became frankly purulent. Repeated smears and cultures were negative for gonococci in every case and at no time could any specific organism be isolated. The urethritis, in most instances, cleared up in less than 2 weeks, but in several cases persisted as long as 6 weeks. Remission of the discharge with subsequent recurrence was observed in 4 patients. Dysuria and frequency accompanied the urethritis in 50% of the cases, while the rest showed asymptomatic discharge. Three patients developed subsequent prostatitis and 1 severe hemorrhagic cystitis. In no case in this series was involvement of the upper urinary tract observed. Circinate lesions of the penis developed in 3 cases. Superficial ulceration of the glans in 1 patient progressed into severe balanoposthitis, but in others the balanitis regressed spontaneously within a week. Only 1 patient demonstrated skin lesions suggestive of keratodermia blennorrhagica. In this case a keratotic eruption appeared on the dorsal surfaces of both hands followed by a herpetiform rash on the palmar surfaces of the feet. The vesicles on the right foot enlarged, coalesced and ruptured, provoking a shallow ulcer. Later a hyperkeratotic lesion developed on the tip of the right third toe.

Purulent conjunctivitis was present in every case and in all but 1 its appearance preceded the onset of arthritis. Generally, the conjunctivitis was of mild or moderate severity with hyperemia, edema and yellow mucopurulent discharge. Superficial keratitis was observed in 1 patient. Usually the severe inflammatory reaction subsided in 3 or 4 days, but in 1 case persisted for 2 weeks. Conjunctival scrapings were consistently negative for inclusion bodies. Cultures of the discharge were either sterile or showed growth of *Staph. albus*.

The cardinal feature of the syndrome in every case was the arthritic phase. Invariably there was a sudden elevation of temperature accompanied by an acute onset of severe to moderate joint pain. The affected joints were red, hot, swollen and tender. Although in 2 cases only a single joint was involved, generally the arthritis was polyarticular and of a migratory type simulating acute rheumatic arthritis. Most commonly the knees and ankles were affected. Less frequently involved were the wrists, hips and interphalangeal finger joints. In 1 unusual case the temporomandibular joint was acutely inflamed. Hydroarthrosis of the knee was present in 6 cases. Roentgenographic studies of the affected joints ordinarily revealed only evidence of soft tissue swelling and the presence of joint fluid. In 2 cases suggestive osteoporosis of the bone ends appeared, although this was not clearly defined. Joint aspirations, carried out in 5 cases, revealed serous fluid with low protein content, 10,000 to 20,000 white cells per c.mm. with a preponderance of polymorphonuclear cells. Cultures of synovial fluid were persistently sterile.

Supplementary laboratory examinations in this survey corresponded more or less to the studies in previous reports. Serologic reactions of the blood were negative in every instance. Electrocardiographic tracings were insignificant in 5 studies. During the acute phase of the illness, leukocytosis ranging from 10,000 to 22,000 per c.mm. was found and a coincidental

elevation of the sedimentation rate was observed. Blood cultures in 2 patients yielded no growth. Because of its unreliability, the complement fixation test for gonorrhea was not employed, although in every case cultures for Neisserian organisms were taken of the exudates from the conjunctiva and urethra and, where possible, of joint fluid. Urine cultures were done on all patients, only 3 of which were positive; 2 for *Staph. albus* and 1 for *E. coli*. Pyuria was present in every case at the outset, but cleared up in at least half the cases before the disease terminated. No animal inoculations were done.

The clinical course of the syndrome appeared to follow a fairly constant pattern. Generally the essential triad was complete within 1 month and the acute phase would reach its zenith in 6 to 8 weeks. Temperature elevations were not pronounced and usually of short duration; in no case accompanied by chill. Following the acute stage, in most cases, involved joints remained swollen, stiff and painful. In only 2 cases was there exacerbation of the acute inflammatory process after initial remission. Total duration of symptoms is presumably subject to considerable variation; entirely accurate follow-up in every case has not been possible. In no case, however, was a patient fully recovered in less than 3 months, and 3 patients were still hospitalized after 4 months of illness.

**Comment.** This curious syndrome with its standard pattern and its variegated clinical complications presents an etiologic problem. Although a variety of causative agents have been suggested, conclusive evidence is lacking to substantiate the position of any as the responsible factor. Several investigators have proposed dysentery organisms, others streptococci and coliform organisms, and Reiter himself, an atypical spirochete. Recently Dienes and Smith[4] isolated a pleuropneumonia-like organism which is apparently associated with genito-urinary infections and may have significant relationship to the Reiter complex. Such bacteria, however, were not discovered in our cases.

This disease would seem to be confined to young men, although 1 dubious case in a female was described by Lever and Crawford.[8] Epidemiology remains obscure, and the present consensus rejects the notions of contagion or nutritional deficiency. In a consideration of geographic distribution, Vallee[13] finds that cases have been reported from western Europe, the United States, and the Pacific Islands.

Pathologic examination of the synovia of the involved joints has been carried out in only 3 cases. Hollander[7] and his associates, who performed arthrotomy and biopsy in 1 patient, report that the synovial membrane was congested and presented a reddish purple appearance. No gross thickening was observed, but several areas of white fibrinous material were present on the surface of the synovial membrane. Microscopic examination revealed a severe inflammatory reaction which was limited to the superficial synovial layers. Their report says the synovial membrane was thrown into large club-like projections in which abundant capillaries were dilated. Each projection was distended by a heavy lymphocyte infiltrate mixed with a few plasma cells and neutrophils. There was no evidence of exudate. The intima was found to be several cells deep. There were no new capillaries and the marked hyperemia consisted of dilatation of the preëxisting capillaries. These findings corroborate the pathologic changes observed in earlier reports by Bauer and Engleman,[1] and by Wepler.[14]

Specific therapy for Reiter's syndrome is unknown. Penicillin, sulfonamides, arsenicals, salicylates and fever therapy have all been recently employed. The great variety of medications tried indicates the inefficiency of each. Effective therapeutic efforts have thus far been limited only to analgesics and palliative measures directed at symptomatic relief.

Despite the unavailability of definite

treatment, prognosis in general is good. No death directly ascribable to the disease has been reported. Although recurrences of the syndrome are known to occur months and even years after the original episode, each attack is generally self-limited in its course without residual structural or functional disorder of the affected systems. In rare instances permanent articular and ocular damage has been reported. Complicating skin lesions are uncommon and invariably are characteristic of keratosis blennorrhagica. Urologic complications are usually of a mild transient nature.

Diagnostic accuracy demands differentiation of Reiter's syndrome from gonorrhea. Clinically the gonorrheal syndrome presents a more severe reaction with chills and high fever. It frequently causes permanent joint damage, but usually responds to chemotherapy. Nevertheless, the only indisputable evidence in differential diagnosis is determined by meticulous bacteriologic studies, since in Reiter's disease gonococci are never found.

**Summary.** 1. Reiter's syndrome is an unusual disease encountered in young males characterized by urethritis, conjunctivitis and migratory arthritis. Skin lesions are occasionally noted; these appear as either keratosis blennorrhagica or balanitis circinata.

2. The etiology of the disease is obscure. No definitive therapy is available.

3. The course of the disease is self-limited, never terminating, however, in less than 3 months. Recurrences are not unusual and may occur years after the initial episode.

4. The disease is perhaps not as rare as has been supposed, since the 12 cases here presented were seen in 2 years by a single observer.

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# A STUDY OF HEPATIC FUNCTION IN ACQUIRED MALARIA*

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Experienced medical men have long noted the apparent transitory hepatitis that so frequently is associated with acquired malaria. Many texts designate a "malarial hepatitis" as a complication to be carefully observed. The term "malarial hepatitis" may be confusing, but the hepatic dysfunction it describes is evident to the physician.

Our study originated in a general hospital early in 1943 because we were impressed by the frequent occurrence of abnormal liver function tests in malarial cases. A search of the literature at that time failed to reveal much concrete evidence substantiating such a clinical occurrence. Most texts of tropical medicine discuss this phase of malaria from a clinical point of view only. During the progress of this study several publications bearing on this problem have occurred. Kopp and Solomon[3] in January 1943, in studying induced malaria, concluded that a transitory effect of diminished hepatic function occurred in 9 patients they observed. Mirsky, Von Brecht and Williams[4] in January 1944 reported a study of 10 patients with acquired malaria and the relationship of serology to cephalin flocculation and concluded that the Kahns were negative and the Hanger tests positive in the absence of therapy.

Kern and Norris[2] in November 1944 studied 100 proven *P. vivax* and *P. falciparum* cases. They concluded: "The outstanding fact to which attention is directed in this report is that demonstrable involvement of the liver occurs in the majority of all cases of malaria and in all stages of the disease, including the earliest acute attack. Furthermore, the incidence is far greater than is commonly realized."

Fredericks and Hoffbauer[1] in June 1945 studied 31 cases of induced malaria in syphilitics and found an increase in serum bilirubin during or after therapy in 14 of 31 cases. There was an increase in the urinary excretion of urobilinogen in 12 of 13 cases tested. There was a positive Hanger test and a retention of bromsulphalein in all cases tested.

Read, Kaplan, Becker and Boyd,[5] in reporting on 300 cases of neurosyphilis treated with therapeutic malaria, discussed the occurrence of malarial hepatitis and pointed out that this complication in mosquito-inoculated cases attests, at least in some instances, to a more specific toxic effect of malaria on the liver than merely by the accidental transmission of an hepatotoxic agent with a blood inoculation.

The laboratory tests reported here represent a careful evaluation in about 250 cases studied in 1943 and 1944. The observations have been repeatedly spot checked since that time both in this country and in New Guinea and the Philippines representing several thousand cases. We believe they accurately represent the picture during the acute phase of infection studied.

**Methods.** Cases were selected carefully to include nothing but *Plasmodium vivax* parasitemia. All cases had smears of peripheral blood examined on entrance to the hospital. As soon as the parasites were demonstrated, therapy with quinacrine hydrochloride was started. Schedules were arranged so that when the patient became afebrile the liver function tests were im-

* The bromsulphalein used in this study was supplied through the courtesy of Hynson, Westcott & Dunning.

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mediately done. Usually this occurred within 2 or 3 days of hospital entrance. Atabrine was prescribed as follows: 2 tablets (3 gr.) every 6 hours for 5 doses, then 1 tablet t.i.d. for 5 days. All of the function tests were done while atabrine was being given for demonstrated parasitemia. All cases of clinical liver disease such as epidemic hepatitis, amebic hepatitis, cirrhosis, etc., were eliminated from the series. The laboratory tests were done by the same personnel under the same conditions. All abnormal tests were rechecked as soon as practical.

mal was taken to be, for cholesterol, 150 to 250 mg. per 100 cc. serum and for the esters 50 to 70% of the total. Hippuric acid (oral method of Quick, p. 76) was regarded normal at 3 to 6 gm. Prothrombin time, determined after the method of Page and Russel (*J. Lab. and Clin. Med.*, **26**, 1366, 1941), was regarded normal up to 23 seconds.

One hundred patients had a series of liver function tests which included the cephalin cholesterol flocculation test, prothrombin time, bromsulphalein, icteric index, hippuric acid, total protein, albu-

TABLE 1.—COMPARISON OF LIVER FUNCTION TESTS IN 2 DIFFERENT GROUPS OF PATIENTS

| Test | Group 1 | | Group 2 | | Total fraction (all cases) | Average % positive |
|---|---|---|---|---|---|---|
| | Fraction (Fig. 1) | % positive | Fraction (Fig. 2) | % positive | | |
| Bromsulphalein | 16/100 | 16 | 25/80 | 31 | 41/180 | 23 |
| Icteric index | 31/100 | 31 | 26/84 | 31 | 57/184 | 31 |
| Hippuric acid | 38/100 | 38 | 39/98 | 40 | 77/198 | 39 |
| Prothrombin | 30/100 | 30 | 27/84 | 32 | 57/184 | 31 |

In the fraction under each column the numerator represents the number of abnormal tests and the denominator the total tests done.

TABLE 2.—CORRELATION OF POSITIVE REACTIONS FOR EACH TEST WITH THE POSITIVE REACTIONS GIVEN BY ALL OTHER TESTS

| | A | B | C | D | E | F | No other positive |
|---|---|---|---|---|---|---|---|
| A—pos. Hanger | 64 | 23/36 | 9/14 | 21/33 | 24/37.5 | 14/22 | 11/17 |
| B—pos. prothrombin | 23/77 | 30 | 5/17 | 12/40 | 10/33 | 4/13 | 1/3 |
| C—pos. bromsulphalein | 10/62.5 | 5/31 | 16 | 9/56 | 7/44 | 3/19 | 1/6 |
| D—pos. icteric index | 21/68 | 12/39 | 8/26 | 31 | 9/29 | 6/19 | 2/6 |
| E—pos. hippuric acid | 24/63 | 10/26 | 6/16 | 9/24 | 38 | 8/21 | 6/16 |
| F—pos. protein | 14/61 | 4/17 | 3/13 | 6/26 | 8/35 | 23 | 3/13 |

Numerator of fraction denotes number, denominator denotes percentage, of positive reactions of test indicated by letter at head of column.

The methods used in this study (except for prothrombin time) may all be found in Simmons & Gentzkow.[6] Pages are noted in parentheses for each specific test. For total protein (method of Army Medical School, page 221) the normal range was taken to be 5.3 to 8.5 gm. per 100 cc. of serum; for globulin, 1.3 to 3 gm. per 100 cc. serum and the normal A/G ratio was taken to be 1.3 to 2.5 to 1. Cephalin-cholesterol flocculation, done after the method of Hanger (p. 77), was regarded as normal up to 2+; icteric index (method of Meulengracht and Bernheim, p. 213) normal up to 11; bromsulphalein (5 mg. per kg. intravenously, p. 73) normal up to 6% retention. For cholesterol and cholesterol esters (method of Schoenheimer and Sperry, p. 211), the normin, globulin and A/G ratio. For the sake of simplicity all of the protein tests have been gathered into 1 group so that we may consider each patient to have had 6 different tests.

Figure 1 is a summary of all the tests in this group and their relationship to each other. It might be pointed out that about one-third of all patients tested showed 3 tests abnormal and about two-thirds showed 2 or more abnormal tests.

A variable number of patients not included in Figure 1 had other tests in addition to the above, or the same tests, that can be used as a check on the evalua-

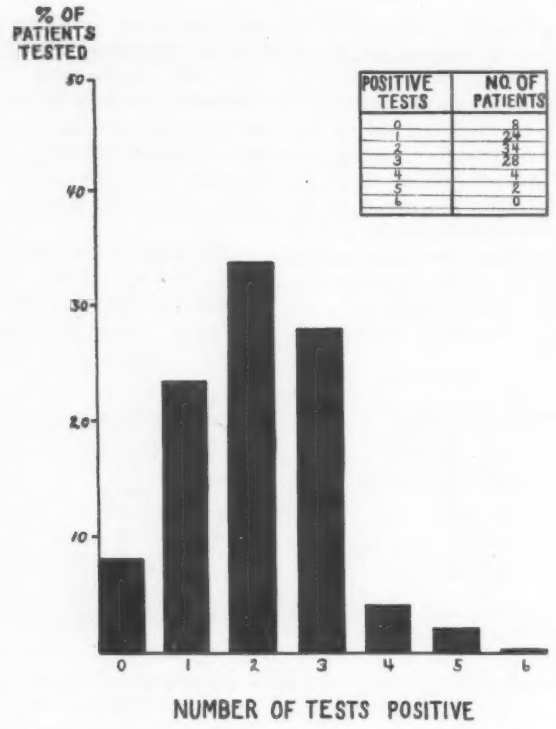


FIG. 1.—COMPARATIVE RESULTS IN PATIENTS OF GROUP 1.

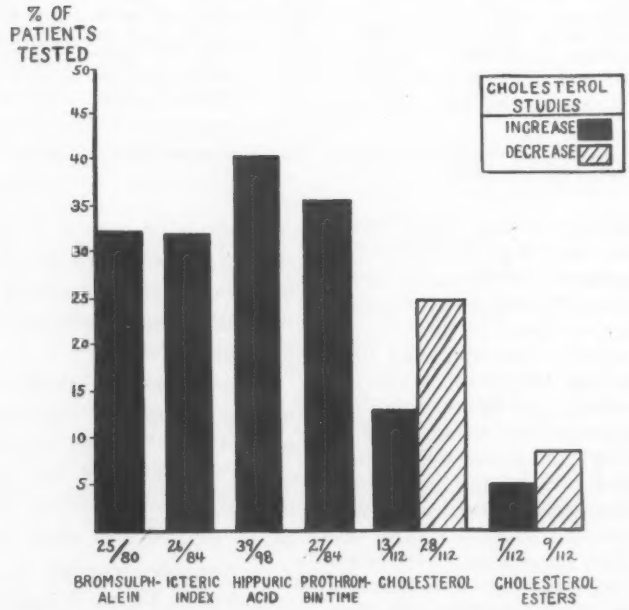


FIG. 2.—Comparative results in patients of Group 2. In the fraction under each column the numerator represents the number of abnormal tests and the denominator the total tests done, *i. e.*, bromsulphalein, 80 tests performed of which 25 were abnormal.

tion of these 100 cases. These are shown in Figure 2.

It can be seen from Table 1 that the comparison between the 2 groups was nearly identical except for the bromsulphalein. We have no obvious explanation for this variant.

An additional 112 patients were examined under the same conditions for cholesterol—cholesterol esters; of these, 28 (25%) showed an increase in total cholesterol, 13 (12%) a decrease in total cholesterol, 9 (8%) an increase in cholesterol esters and 7 (6%) a decrease in cholesterol esters.

In analyzing the results, it is of interest to note that about three-fourths of the positive tests were correspondingly matched by other positive tests as demonstrated in Table 2.

**Summary.** One hundred cases of acute acquired malaria under atabrine therapy received a series of liver function tests. In addition, another group of about 150 patients were tested with random liver function tests and the results of both groups compared.

Our personal observations in the United States, New Guinea and the Philippines, continuing these studies but not herein reported, have supported the conclusions of this report in every way.

Although long range follow-up studies were impossible, under our conditions, it is our clinical opinion that the hepatic dysfunction demonstrated is transitory. It rarely, if ever, leaves permanent liver damage with the possible exception of cases where previously diseased livers existed and in which extension of the process may occur. This may result in more rapid development of the chronic cirrhotic liver occasionally seen from the tropics.

**Conclusions.** 1. Approximately one-third of all acute acquired malaria cases under atabrine therapy are shown to have demonstrable hepatic dysfunction as evidenced by standard liver function tests.

2. Less specific tests, such as the cephalin flocculation test, are positive (3+ to 4+) in about two-thirds of the cases.

3. None of the liver function tests used was accurate when used alone as an index of hepatic dysfunction.

4. A significant number of clinical cases of acquired benign tertian malaria under atabrine therapy show definite evidence of hepatic dysfunction.

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# PROTEIN DEPLETION AND HEPATIC FUNCTION IN THE DOG

## RATIONALE OF METHIONINE IN THERAPY

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It is now generally accepted that protein depletion renders the liver more susceptible to damage by hepatoxic agents and that methionine and cystine are the specific protein factors which will protect susceptible animals.[7,9,10,15,16,17] The mechanism of this protective action is not clear, but it has been shown that the liver of protein depleted dogs is not only depleted of protein but is relatively more deficient in sulfur (S) than nitrogen (N) (increase in N/S), and that this ratio is restored toward normal by methionine or cystine.[17] This protective action is probably independent of the lipotropic action of methionine because choline alone has been found without protective effect against chloroform liver damage in dogs[17] and rats.[6] However, a simultaneous choline deficiency with fatty liver unquestionably renders the liver even more susceptible to damage.

It is known that a small supplement of methionine or cystine will spare the N of body protein stores in dogs on a very low protein diet[18] or greatly increase the biologic value of diets quantitatively or qualitatively,[13] inadequate in protein. But it is not generally recognized that the N sparing effect of a methionine supplement becomes negligible when the casein content is increased.

Expecting protein depletion to result in impaired liver function, we sought to study the effects of simple protein depletion and of methionine supplementation on hepatic function using a modification of the bilirubin clearance test of Von Bergmann and Eilbott.[23] At the same time because of controversial reports of the therapeutic value of methionine in liver injury and protein deficiency states, we have made some observations on the N sparing effect of methionine when added to diets of varying protein content.

**Methods.** The dogs observed in the experiments of Table 1 were healthy mongrels on (1) a diet of mixed table scraps (kennel diet) which maintains weight and keeps them in good condition; (2) a very low protein diet containing sucrose 72.2%, Crisco 14.9%, Mazola oil 6.5%, cod-liver oil 1.4%, yeast powder (Fleischmann's Type 200-B) 0.7%, powdered liver extract (Lilly, H 8083) 0.7%, Wesson salt mixture 4.6%, calcium phosphate 4.6%. The diet was fed at a level to provide 70 calories per kilo body weight daily and was supplemented with 400 mg. choline chloride and 25 mg. of nicotinic acid daily. The dogs of Table 2 were maintained on the low protein, high fat diet of Hough and Freeman[11] which contains no choline except that which may be present in the yeast used.

The dogs of Table 3 were maintained on the very low protein diet described above with replacement of an approximately isocaloric portion of the diet by commercial casein in the indicated amounts. When the urinary N excretion became fairly constant, the daily supplement of 1 gm. of dl-methionine was started. The bilirubin clearance of Tables 1 and 2 were carried out according to Von Bergmann and Eilbott with modifications.[23] Bilirubin (Eastman Kodak) was given intravenously in solution prepared by dissolving 3 mg. of bilirubin

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TABLE 1.—BILIRUBIN CLEARANCE UNAFFECTED BY PROTEIN DEPLETION

| Dog No. | Dietary regime | Plasma protein level (gm.%) | Plasma bilirubin retention (%) |
|---|---|---|---|
| | *Normal Dogs* | | |
| 1 | 4 days 20 gm. casein daily after low protein diet | 5.20 | 17.9 |
| 2 | Salmon bread | 7.10 | 16.7 |
| 3 | Kennel diet | 6.82 | 16.8 |
| 4 | Kennel diet | 6.23 | 14.1 |
| 5 | Kennel diet | 6.21 | 22.4* |
| 6 | Kennel diet | .. | 18.9 |
| 7 | Kennel diet | 6.05 | 22.8† |
| 8 | Kennel diet | 6.59 | 20.0 |
| 9 | Kennel diet | 6.37 | 15.3† |
| 9 | Kennel diet | 6.53 | 26.7‡ |
| 10 | Beef liver 150 gm. per day plus low protein diet | 5.75 | 19.4 |
| | *Protein Depleted Dogs* | | |
| 1 | 10 day fast—9 wk. non-protein diet | 4.70 | 16.1 |
| 3 | 7 day fast—7 wk. non-protein diet | 4.84 | 19.3 |
| 7 | 4 day fast—7 wk. non-protein diet | 5.05 | 18.4 |
| 9 | 10 day fast—9 wk. non-protein diet | 4.67 | 18.0 |
| 11 | 7 day fast—7 wk. non-protein diet | 4.23 | 19.0 |
| 12 | 4 day fast—7 wk. non-protein diet | 4.94 | 20.7 |

* After 72 hours fast.
† After 48 hours fast.
‡ After 10 day fast.

TABLE 2.—BILIRUBIN CLEARANCE ON CHOLINE DEFICIENT, LOW PROTEIN DIET

| Dog No. | Weeks on diet: 2 P.P. level (gm. %) | 2 Bil. ret. (%) | 4 P.P. level (gm. %) | 4 Bil. ret. (%) | 5.5 P.P. level (gm. %) | 5.5 Bil. ret. (%) | 6.5 P.P. level (gm. %) | 6.5 Bil. ret. (%) | 9 P.P. level (gm. %) | 9 Bil. ret. (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| 3 | 5.21 | 19.8 | .. | .. | .. | .. | .. | .. | 4.58 | 33.4 |
| 4 | 5.71 | 16.2 | 4.93 | 30.2 | 5.18 | 37.2 | 4.97 | 45.0 | | |
| 8 | 5.44 | 19.9 | .. | .. | .. | .. | .. | .. | 5.07 | 46.7 |
| 9 | 5.61 | 32.4 | .. | .. | 5.08 | 35.8 | 4.82 | 32.4 | | |

TABLE 3.—NITROGEN SPARING ACTION OF DL-METHIONINE ON HIGH AND ON LOW N INTAKE*

Dog 12 (wt. 11.7 kilos)—high protein intake (12.7 gm. N per Periods 1 and 2; 13.6 gm. N per Period 3 through 5)

| Period 48 hrs. | 1 | 2 | Basal diet | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| T N urine | 8.18 | 7.48 | + dl-Methionine | 7.12 | 7.43 | 9.18 | |
| % urea-$NH_3$ N | 89.40 | 90.00 | 1 gm. daily | 92.20 | 90.70 | 89.40 | |

Dog. 12 (wt. 11.4 kilos)—moderate protein intake (3.46 gm. N per period)

| Period 48 hrs. | 1 | 2 | Basal diet | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| T. N. urine | 3.53 | 3.27 | + dl-Methionine | 2.09 | 1.95 | 1.90 | |
| % urea-$NH_3$ N | 77.60 | 76.80 | 1 gm. daily | 63.00 | 70.10 | 63.90 | |

Dog. 12 (wt. 10.5 kilos)—very low protein intake (0.66 gm. N per period)

| Period 48 hrs. | 1 | 2 | Basal diet | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| T N urine | 2.29 | 2.18 | + dl-Methionine | 1.51 | 1.18 | 1.29 | 1.18 |
| % urea-$NH_3$ N | 75.10 | 70.30 | 1 gm. daily | 60.70 | 61.50 | 52.00 | 51.10 |

Dog. 13 (wt. 11.4 kilos)—high protein intake (14.1 to 14.2 gm. N per period)

| Period 48 hrs. | 1 | 2 | Basal diet | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| T. N. urine | 9.16 | 9.42 | + dl-Methionine | 9.60 | 10.27 | 10.78 | 11.94 |
| % urea-$NH_3$ N | 92.20 | 94.20 | 1 gm. daily | 93.90 | 88.80 | 92.70 | 90.50 |

Dog 13 (wt. 11.7 kilos)—moderate protein intake (3.98 gm. N per Period 1 and 2; 4.19 gm. N per Period 3 through 6)

| Period 48 hrs. | 1 | 2 | Basal diet | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|
| T N urine | 3.83 | 3.52 | + dl-Methionine | 2.71 | 2.06 | 2.42 | 2.45 |
| % urea-$NH_3$ N | 78.70 | 82.80 | 1 gm. daily | 77.60 | 72.30 | 71.80 | 72.70 |

* N intake does not include 0.19 gm. N per period from methionine N.

per kilo body weight in 20 to 30 cc. of 1% sodium carbonate solution. No untoward reactions were produced. After exactly 5 minutes and 60 minutes had elapsed from the time of injection, samples of blood were drawn from the opposite external jugular vein and mixed with 1.4% sodium oxalate solution as anticoagulant. After centrifugation, aliquots of the clear plasma were treated according to the method of Malloy and Evelyn[14] for the determination of bilirubin. Color intensity was read in a Klett photoelectric colorimeter with a 54 filter. Lipemic or hemolyzed samples of plasma were rejected. The bilirubin retention figures in Tables 1 and 2 represent the per cent of bilirubin concentration present at 60 minutes in comparison with the 5 minute value as 100%.

Plasma protein concentrations and total urinary nitrogen determinations were made by macro-Kjeldahl. Urea-ammonia nitrogen was estimated by aëration and titration after urease treatment.

**Results and Discussion.** There were only insignificant changes in bilirubin clearance in the dog with protein depletion resulting from 8 to 10 weeks maintenance on a very low protein diet presumably adequate in calories and vitamins including choline (Table 1). In 2 unrecorded experiments in such protein depleted dogs, the addition of methionine to the diet several days before and intravenous injection immediately before the bilirubin clearance test failed to reduce the bilirubin clearance values below the normal values obtained without methionine. Furthermore in several animals, determination of prothrombin time by the method of Quick[20] showed no measurable change resulting from protein depletion of this duration. In the protein depleted dog there is thus a striking disparity between increased susceptibility to damage by hepatoxic agents and continued ability to clear the blood of bilirubin, or to form prothrombin. This is at variance with reports[5,11,12,24] claiming rapidly developing impairment of liver function with protein depletion. The composition of the diets used in these cited experiments was such that the impaired hepatic function reported to result from protein depletion *per se* may indeed have been the result of choline deficiency. In addition the dogs in many of these experiments rapidly became partially or almost totally anorexic and suffered large weight losses. The combined effects of protein depletion, choline deficiency and inanition cannot be ascribed solely to protein depletion. In fact, several of the animals cited in Table 1 show that prolonged fasting alone may be associated with decreased clearance of bilirubin from the plasma. Table 2 shows how the complication of choline deficiency resulting from the high fat, low protein diet of Hough and Freeman[11] produces early impairment of bilirubin clearance and indicates that choline deficiency is an added liability which may be superimposed on and complicate simple protein deficiency.

Current interest in the possible application of methionine and cystine to therapy has led to conflicting claims of its value. The best clinical results have been reported[1,4,22] in the treatment of hepatic injury resulting from exposure to chemical poisons and in the therapy of cirrhosis of the liver. The value of methionine in the treatment of infectious hepatitis is difficult to assess from reports[19,21,25] in which treatment may have been started too late to be of decisive value, or in which methionine was superimposed on a diet already containing considerable methionine in the form of dietary protein.

Table 3 contains evidence that a methionine supplement has little or no significant continued N sparing effect when the diet already contains large amounts of protein of good methionine content. In contrast to this is the distinct N sparing effect of methionine when added to a diet of moderate or very low protein content (Dogs 12 and 13). Wherever methionine supplementation spares N it does so at the expense of the urea-ammonia N fraction.

On the basis of these experimental findings it appears that methionine supplementation of diets already containing

large amounts of methionine and cystine in food protein may be unwarranted and even wasteful. By the same token, where digestion and absorption of such a high protein dietary are unimpaired, it seems unreasonable to expect any "supernormal" protective action from large supplements of methionine. Indeed Drill and Loomis[2] have been unable to demonstrate any "superprotection" against carbon tetrachloride liver damage when methionine is added to high casein diets.

To avoid possible untoward effects of great methionine overdosage,[3] it seems desirable to limit the total daily methionine intake to an amount equivalent to 1 to 1.5 gm. (per kilo body weight) of the best dietary protein. Using whole egg protein with 1.5% S as a basis for calculation, a 70 kilo man would require the equivalent of 4.9 to 7.4 gm. of methionine per day. On another basis, assuming a daily N loss of 10 to 20 gm. per day and a daily S loss of 0.63 to 1.25 gm. (N/S = 16), then approximately 3 to 6 gm. of methionine should be adequate to replace the daily total S loss. The recently formulated minimal protein requirement for healthy normal males[25] would place the minimum intake level even lower.

The therapeutic use of methionine appears indicated: (1) as early as possible and continuously in any case of acute hepatic disease particularly toxic hepatitis, especially where the status of protein nutrition is difficult to assess, and when during illness the dietary protein intake is poor or negligible; (2) where protein depletion is known to exist; (3) where the diet protein intake is suboptimal quantitatively by choice, or through inability to ingest, digest and absorb large amounts of good food protein; (4) where the diet protein intake is suboptimal qualitatively as a result of restriction to those proteins comparatively low in S content.

**Summary.** 1. Evidence is presented that simple protein depletion uncomplicated by choline deficiency produces no significant change in the ability of the dog to clear injected bilirubin from the blood. This is in distinct contrast to the greatly increased susceptibility of the protein depleted dog to hepatoxic agents such as chloroform.

2. A high fat, low protein diet deficient in choline is associated with early impairment of ability to clear injected bilirubin from the blood.

3. The N sparing acting of methionine supplements in the dog varies with the total methionine content of a protein dietary in the dog. Maximal effect is observed where the protein intake is relatively low. Virtually no continued effect is seen where the diet already contains large amounts of methionine as protein.

The implications of these observations for the therapeutic use of methionine are indicated.

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# PERSISTENT FAMILIAL (NON-SPECIFIC) SEROLOGIC FLOCCULATION REACTIONS FOR SYPHILIS SUGGESTING AN HEREDITARY MECHANISM*

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Is there such an entity as persistent, familial, non-specific reaction to a serologic test for syphilis? The existence of non-specific positive reactions is now generally accepted. In recent comprehensive reviews by Beerman[2] and Davis[6] a variety of causes are recorded. The rôle played by immunizations and intervening infections in producing transient positive serologic reactions in persons known to have been previously negative receives considerable attention. Beerman notes that recently there have been occasional reports of familial non-specific positives consequent to an infectious disease. Neither Beerman nor Davis, however, record any report of "idiopathic" false positive tests persisting in several members of a family. Stokes, Beerman and Ingraham[13] do not include in that portion of their text which deals with non-specific positives any instance of such an observation. Stokes, however, has expressed himself as follows: "Why should there not be such a thing as familial false positive reactiveness, and why indeed should it not even have a gene distribution in association with blood types?"[12]

The mechanism of the production of a non-specific positive remains undetermined. Malloy and Kahn[8] stated that "it appears that the difference between non-syphilitic and syphilitic serum is one of degree rather than kind; that it is quantitative rather than qualitative." A similar conclusion was reached by Barnett, Jones and Kulcher.[1] Mohr and his associates,[9] however, believe that normal reagin differs qualitatively from that of syphilitic serum. They present records of 9 individuals who were thought to give non-specific positive reactions, and from the study of these cases they feel that normal reagin may at times be present in sufficient concentration to give non-specific positives. The difference of opinion expressed in these 2 views is a fundamental consideration in any approach to the problem of how these reactions occur.

Familial occurrences of non-specific positive reactions, transient in duration and associated with acute infections, have been reported. Zugar and Moffat[14] record observations obtained on 3 brothers who had afebrile upper respiratory infections. Positive Kahn tests were obtained on the serum of each one, but their mother's serum was negative. One month later the reaction was negative in each instance. Lindau[7] reports the data on a family of 6. Both parents and 2 of the 4 children showed non-specific reactions to the Kahn and Wassermann tests following attacks of bronchitis. Within a short time, however, all the positive reactions became negative. Smith[11] studied 2 brothers whose serologic reactions to the Wassermann and sigma tests were positive following mumps. The sera of the parents gave negative reactions. One of the boys died of encephalitis due to mumps; the other one had a negative serologic reaction to both tests 4 months after the first determination. The cases cited by Mohr

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and his associations do not include any observation of a familial non-specific positive. The majority of their cases showed a transient false positive reaction. In 1 instance the positive reaction persisted for 6 months but further observations were not recorded.

The query at the beginning of this report was prompted by observations continued over a 2 year period on the members of a family. During this period the sera of several members showed a persistently positive reaction to 1 type of test and the reactions were felt to be non-specific. In addition to the finding of a familial incidence of a persisting non-specific positive reaction, some data were obtained which suggest the possible existence of an hereditary mechanism by which the non-specific positive factor was transmitted from 1 parent to several of her children.

**Family Study.** In February 1944, V. F., a 35 year old white female of Italian birth and 4 to 5 months pregnant, was seen in the prenatal clinic of the Lankenau Hospital. The routine prenatal serologic tests for syphilis showed a positive Kline test but a negative complement fixation reaction. A repetition of the serologic study 2 weeks later yielded identical results, and the patient was referred to the syphilis clinic.

The past history of the patient was not particularly helpful in evaluating her condition. There had been 4 previous pregnancies. The first 3 resulted in normal, full-term deliveries, but the fourth terminated by miscarriage at the 3rd month. The patient had been in the United States for about 20 years. There was no history of any treatment for syphilis. The only previous serious illness had been malaria at the age of 15 while she was still in Italy. The physical examination was not remarkable except for carious teeth. There was no evidence of congenital syphilis. Although it was not felt that a definite diagnosis had been established, it was considered advisable to begin treatment because of the pregnancy and its duration. From March 13, 1944, through June 27, 1944, the patient received weekly injections of neoarsphenamine, maximum dose 0.45 gm., except for 2 weeks when she did not attend clinic. A living, normal, full-term female infant was delivered on June 29, 1944. Subsequently the mother received rather irregular treatment during the next year.

Soon after the patient was first seen in the syphilis clinic an investigation of the family was done as a routine procedure. Considerable interest was aroused by the fact that the serum of each of the other 3 children gave a positive reaction to the Kline test, but, like their mother, a negative complement fixation reaction. Neonatal serologic studies on the child born in June 1944 resulted in negative results by both tests. Similar negative observations on the serum of the father were reported when he was studied later in the year. The results of all the routine examinations on the sera of the various members of the family are summarized in Table 1. For clarification a specimen of serum from each member of the family was tested at the Laboratory of the Graduate Hospital by quantitative serologic tests developed by Boerner and Lukens.[4,5] Flocculation and fixation of complement were studied. Multiple examinations were performed subsequently and the results are tabulated in Table 2. On the first examination the sera of the mother and the 3 older children showed very low units of complement fixation, values within normal range, but units of flocculation in each instance were sufficiently high to be accepted as definitely positive. Subsequently these results were duplicated twice on each of these 4 persons. The results of the second study on the serum of James F. were not a significant deviation, as the serum was still in the doubtful group according to the classification of Boerner.[3] In this classification $2\frac{1}{2}$ units of fixation of complement are required for positivity, and 1 flocculation unit is required for positivity. The serum of the father showed no flocculation or fixation of complement when tested by the methods of Boerner and Lukens. The serum of the youngest child, Jean F., also gave negative results by this method when she was 11 months old.

A study of Table 1 shows consistency in the pattern obtained by the routine serologic tests on the sera of the mother and the 3 older children, as seen in the first and also the subsequent examinations. In none of the studies was there any evidence of reaction to the complement fixation test, but there was always some reaction to the Kline

test. The quantitative aspects are better illustrated by the methods of Boerner and Lukens. Incidentally, none of the 3 older children showed any evidence of congenital syphilis. The repeatedly negative results obtained by both routine tests on the serum of the father contrast with the observations on these others. If the family is grouped according to these results, the father and the youngest child appear to form one group,

TABLE 1.—RESULTS OBSERVED WITH BOERNER-LUKENS SIMPLIFIED COMPLEMENT FIXATION TEST AND KLINE DIAGNOSTIC TEST

| | B. F. Father<br>Born 1900<br>Type O<br>Rh Pos. | V. F. Mother<br>Born 1909<br>Type A<br>Rh Pos. | James<br>Born 1925<br>Type A<br>Rh Pos. | Josephine<br>Born 1929<br>Type A<br>Rh Pos. | Gloria<br>Born 1933<br>Type A<br>Rh Pos. | Jean<br>Born 6/29/44<br>Type O<br>Rh Pos. |
|---|---|---|---|---|---|---|
| February 1944 | ... | C.F. Neg.<br>Kline +3 | | | | |
| February 1944 | ... | C.F. Neg.<br>Kline +4 | | | | |
| March 1944 | ... | ... | Wass. Neg.<br>Kline +2 | Wass. Neg.<br>Kline +2 | Wass. Neg.<br>Kline +2 | |
| June 1944 | ... | ... | ... | ... | ... | Wass. Neg.<br>Kline Neg. |
| August 1944 | ... | C.F. Q.N.S.<br>Kline +2 | | | | |
| November 1944 | Wass. Neg.<br>Kline Neg. | | | | | |
| November 1945 | Wass. Neg.<br>Kline Neg. | | | | | |
| February 1946 | Wass. Neg.<br>Kline Neg. | C.F. Neg.<br>Kline +1 | ... | Wass. Neg.<br>Kline +2 | Wass. Neg.<br>Kline +1 | |

All tests performed in the routine serologic laboratory of the Lankenau Hospital, Philadelphia.

TABLE 2.—BOERNER'S GROUPING AND CLASSIFICATION BASED ON FLOCCULATION AND FIXATION OF COMPLEMENT UNITS (BOERNER-LUKENS METHODS)

| | B. F. Father | V. F. Mother | James | Josephine | Gloria | Jean |
|---|---|---|---|---|---|---|
| November 1944 | ... | Fix. Comp. ¼<br>Floc. 8<br>Class 5<br>Group 2 | | | | |
| December 1944 | ... | ... | ... | Fix. Comp. ¼<br>Floc. 4<br>Class 5<br>Group 2 | Fix. Comp. ¼<br>Floc. 4<br>Class 5<br>Group 2 | |
| January 1945 | ... | ... | Fix. Comp. ½<br>Floc. 8<br>Class 5<br>Group 2 | | | |
| April 1945 | ... | Fix. Comp. 0<br>Floc. 4<br>Class 5<br>Group 2 | Fix. Comp. 1¼<br>Floc. 1<br>Class 7<br>Group 2 | | | |
| May 1945 | ... | ... | ... | ... | ... | Fix. Comp. 0<br>Floc. 0<br>Class 1<br>Group 1 |
| July 1945 | ... | ... | ... | Fix. Comp. ½<br>Floc. 8<br>Class 5<br>Group 2 | Fix. Comp. 0<br>Floc. 8<br>Class 5<br>Group 2 | |
| August 1945 | ... | ... | Fix. Comp. 1<br>Floc. 4<br>Class 5<br>Group 2 | | | |
| November 1945 | Fix. Comp. ½<br>Floc. 0<br>Class 1<br>Group 1 | | | | | |
| February 1946 | ... | Fix. Comp. ½<br>Floc. 8<br>Class 5<br>Group 2 | ... | Fix. Comp. 1<br>Floc. 8<br>Class 5<br>Group 2 | Fix. Comp. 1<br>Floc. 8<br>Class 5<br>Group 2 | |

All tests performed in the laboratory of the Graduate Hospital, Philadelphia.

while the mother and the 3 older children form a second.

Efforts to study further the mother and her own family for evidence of syphilis were unrewarding. No other members of her family were here in the United States. She had little knowledge of the medical histories of her family, but she had never known of the administration of intravenous therapy to any of them while she was in Italy. One previous record of a serologic test for syphilis on the mother was obtained. This was in 1933, when a Wassermann test had been performed at another hospital, presumably before the birth of the third child. This was reported as negative. There was no record of the performance of a Kline or any other flocculation test at that time.

Neurath of the Department of Biochemistry, Duke University School of Medicine. When tested by his method of globulin fractionation[10] the sera of the mother and Gloria gave non-specific positive reactions. The test on the serum of Josephine, however, showed an inconclusive result. A second examination of the serum of the mother gave a similar result to that first obtained. The close grouping of 11 of 12 examinations in Class 5 would seem to be more than a coincidence. The single exception is still in Group 2, the doubtful class according to Boerner's classification.

During all this study there was no history of intercurrent infection in the members of the family or of any immunizations. The impression was strengthened that we were

*Parents*

| *Father* | *Mother* |
|---|---|
| Age 46 | Age 37 |
| Type O | Type A |
| Rh positive | Rh positive |
| C.F.* negative | C.F.* negative |
| Floc. negative | Floc. positive |

*Children*

| James | Josephine | Gloria | Jean |
|---|---|---|---|
| Age 18 | Age 17 | Age 12 | Age 2 |
| Type A | Type A | Type A | Type O |
| Rh positive | Rh positive | Rh positive | Rh positive |
| C.F.* negative | C.F.* negative | C.F.* negative | C.F.* negative |
| Floc. positive | Floc. positive | Floc. positive | Floc. negative |

* C.F. = Complement fixation test.

A study of the blood groups was conducted on the entire family. The father and the youngest child were found to be in Group O while the mother and the 3 older children were in Group A. This division correlated exactly with the division of the family according to serologic tests for syphilis. The study of the Rh types, however, did not show a correlation, as all were Rh positive.

An analysis of Table 2 gives some interesting figures. Twelve examinations were done by the method of Boerner and Lukens on the sera of the mother and the 3 older children. Of these 12, 11 gave results which fell in Class 5, Group 2, according to the classification of Boerner, which offers 13 possible classifications.

Further confirmation of our assumption that the serologic reaction of the mother and 3 of the children were non-specific positive was obtained through tests done by Dr. Hans

dealing with an hereditary factor which caused a persistent, non-specific false positive reaction to flocculation tests for syphilis. The correlation of the blood groups with the serologic reactions seemed to relate this factor with a known hereditary phenomenon. The serologic reaction and blood groups of the entire family are summarized above.

**Comment.** Apparently no previous reports on this subject have recorded persistence of non-specific positive reactions for a 2 year period. Non-specific positive reactions seem to be related to extrinsic causes, such as infections or immunizations. The rare familial incidence reported previously have all been attributed to infections. The family whose study is being reported here showed no evidence of syphilis, and they had experienced

neither recent infections nor immunizations. The pattern of the positive serologic reactions is interesting in that only the flocculation tests were positive. A possible mechanism of hereditary transmission of the factor responsible for the non-specific positive reactions is suggested by the correlation of the blood groupings and the serologic reactions. The exact nature of this factor is not apparent from the present study.

It is unfortunate that the inaccessibility of the mother's family prevented further investigation in that direction. Any future offspring of the 3 children involved would furnish an opportunity to extend the hereditary study.

This investigation further emphasizes the importance of a prolonged serologic study and clinical evaluation of all cases in which there is any doubt whatever concerning the existence of syphilis. Furthermore the clinical evaluation should in some cases be extended to the entire family.

**Summary.** The 6 members of an Italian family were studied for 2 years. Of the 6, 4 showed a persistently positive flocculation reaction to serologic tests for syphilis although there was no evidence of syphilis in any one of them. The reactions were regarded as biologic false positives. The correlation of the blood groupings with the serologic reactions suggested an hereditary mechanism as a possible explanation of the existence of the observed serologic phenomena. No further information regarding the exact nature of the factor responsible was obtained.

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# SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD OCCURRING IN IDENTICAL TWINS*

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Despite the fact that there exists a satisfactory treatment for pernicious anemia and its neural complications, many features of these 2 conditions remain unexplained. Among these is the significance of inheritance as an etiologic factor.

While pernicious anemia seems to have an heredo-familial incidence and even gastric achlorhydria has been shown to occur in families,[14] very few cases of nervous system involvement with heredo-familial tendencies have been recorded. S. A. Kinnier Wilson[16] remarked, "The curious feature of these and other genealogies marked by transmission of Addisonian anemia is the absolute rarity with which the nervous syndrome makes an appearance. Among all the 199 cases from the National Hospital, heredity seemed to play no part, and not 1 of the kind has been personally observed."

In 1912, Willson[15] described a woman who died at the age of 43 with pernicious anemia and subacute combined degeneration. Her sister died of "tabes with anemia" and her maternal aunt died of pernicious anemia. Hurst[4] (1924) found a man with the nervous disease and anemia whose father, brother, paternal uncle and paternal grandfather had died of pernicious anemia. He later[5] reported a man with subacute combined degeneration whose paternal grandfather had pernicious anemia, and a woman with the cord disease whose mother had pernicious anemia. Maclachlan and Kline[8] traced a family tree through 5 generations in which there were 4 cases living with pernicious anemia, 7 living with secondary anemia, and 13 who had died of "anemia." In the third generation of this family there were 4 cases with possible nervous system involvement. Dorst[2] studied a family through 3 generations. One woman died at the age of 46 with both pernicious anemia and subacute combined degeneration. She had 3 daughters who died of pernicious anemia and subacute combined degeneration and 1 son who died of pernicious anemia. Liepelt[7] described pernicious anemia and spinal cord involvement in a mother and daughter. Johannessohn[6] and Tschernin[12] also reported briefly on the familial incidence of subacute combined degeneration.

Ungley and Suzman[13] reported a family in which 2 brothers died of subacute combined degeneration, 1 brother had pernicious anemia and 1 sister died of pernicious anemia. The sister had a daughter who died with subacute combined degeneration. They also described 2 sisters, 1 of whom had died of pernicious anemia and the other was then under treatment for subacute combined degeneration. Witts[17] reported on 2 sisters who had died of pernicious anemia. They had a healthy sister who had 2 daughters, 1 with pernicious anemia and the other with both pernicious anemia and subacute combined degeneration. In a study of the interrelation of pernicious and idiopathic anemias, Heath[3] referred to a family in which 3 sisters had pernicious anemia and subacute combined degeneration. Another sister died at 35 with what was "presumably pernicious anemia."

Ranson and Reback[10] gave an extensive report of a young man who had severe pernicious anemia with diffuse involve-

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ment of the nervous system and who recovered with liver therapy. This man's mother died of pernicious anemia and subacute combined degeneration and his paternal uncle also had both the anemia and spinal cord involvement.

Despite Wilson's skepticism as to the heredo-familial basis of subacute combined degeneration, the above reports would seem to suggest that such an etiologic factor might exist. To add to this data, we wish to record our observations on identical twins who developed the syndrome of posterolateral sclerosis with gastric achlorhydria and who both responded satisfactorily to the administration of liver extract.

**Report of Cases.** *Family History.* Nothing is known about the maternal grandparents of our patients. The paternal grandfather died in 1905 at the age of 75 from unknown causes. The paternal grandmother is still living in her 90's. There was no history of anemia or nervous system disease in any of the uncles or aunts. The father of the twins died in 1937 at the age of 83. The cause of his death was not accurately known. Their mother died in 1901 at the age of 40 from bronchopneumonia. The first born child was a sister who lived only 3 months. She died of a "leaking heart." Another older sister died at the age of 54, in 1941, because of complications related to an abdominal "growth."

Both of our patients are married. C. W. has 2 daughters (22 and 21 years old) both of whom are well. F. W.'s marriage has been without issue.

CASE 1. C. W., a white male, born May 22, 1890, began to notice "numbness and tingling" in his fingers and toes in the mornings, but were said to have disappeared after several months. In October 1938, the "numbness and tingling" returned and his physician noted some signs of incoördination in his lower extremities. His blood count was "normal" at this time.

In August 1939, the patient had a left inguinal herniorrhaphy at the Philadelphia Naval Hospital. In October 1939, the patient began to notice more unsteadiness of his gait. He staggered at times and found it harder to walk at night. He was considerably fatigued and fell asleep readily. He had episodes of spontaneous crying. Because of these symptoms he reëntered the Naval Hospital where the following observations were made: The general *physical examination* showed multiple small lipomata of the skin of the extremities and body, but was otherwise unimportant.

The *neurologic examination* showed the cranial nerves to be intact. The patient's gait was ataxic and he walked with a wide base. The Romberg test was positive. There was some dyssynergia and dysdiadokokinesia of all extremities. There was impairment of performance of skilled acts with his fingers. Muscle power, tone and volume were not disturbed. Touch seemed to be impaired in both feet. Position sense was lost in the toes. Vibration sense seemed to be intact, although later examination showed some impairment in the feet. Pain sensation was preserved throughout. Later on during his stay in the hospital, stroking the soles of both feet had painful cutting and burning qualities. The deep reflexes and periosteal reflexes in the upper extremities were equally hyperactive. The patellar and Achilles reflexes were absent. The lower abdominal reflexes were absent. No pathologic reflexes were noted.

The patient showed some mild confusion at times, was mentally dull, and poorly coöperative. He showed no emotional disturbances and no memory defects at any time.

Blood counts (Nov. 15, 1939): red blood cells, 4,360,000; hemoglobin, 14 gm. (84%); white blood cell count, 6200 (polymorphonuclears 65%, lymphocytes 27%, monocytes 8%). All other blood counts were relatively the same. Red blood cells were reported as normal in size and shape. The hematocrit on November 16 was 37 and on November 28 was 40.

The urinalyses were essentially negative. The blood Kahn tests were negative. A chest roentgenogram showed some emphysema of the pulmonary bases. The electrocardiogram revealed a moderate left axis deviation.

Gastric analysis with histamine on November 26 showed absence of free hydrochloric acid.

The cerebrospinal fluid showed protein, 20 mg. %; sugar, 68 mg. %; negative Kahn, colloidal gold of all zeros, and 1 to 2 cells. The cerebrospinal fluid was under normal

pressure and the Queckenstedt test was negative.

The patient was started on liver therapy in December 1939. He improved slowly but steadily. In the early weeks of his hospitalization, he had become weaker, was scarcely able to walk, and was finally confined to bed; but by the end of December he was able to walk with assistance. When discharged from the hospital in June 1940, he walked without assistance although the neurologic examination showed little change. He continued liver therapy at home and by January 1941 was able to return to "flagging" on the railroad. By October 1945 he was able to return to his original job as a brakeman, which he has held to date.

A neurologic examination on April 7, 1946, by one of us (G. S.) showed the following: The cranial nerves were intact. The patient's gait was steady but there was a little instability noted on turning. In the Romberg test slight swaying was still present. There was a little ataxia on the heel-to-knee test bilaterally. Pain, touch, temperature, vibration and position sense were intact throughout. All of the deep and superficial reflexes were hyperactive throughout with a transient ankle clonus on the right side. The abdominal reflexes were present. A right Hoffman sign was the only abnormal reflex noted, although plantar flexion was absent on the left side.

The patient is still receiving "1 cc. of crude liver extract" intramuscularly each week and takes 10 drops of HCl before meals.

CASE 2. F. W., the identical twin brother of C. W., was admitted to the Neurological Section of the University of Pennsylvania Hospital on Oct. 3, 1944. For 4 years the patient had been complaining of "trembling" of his hands, especially the right. He began to have tingling sensations in his fingers and feet in August 1944. His gait became unsteady. He had noticed no increased difficulty in getting around in the dark.

The general physical examination was negative except for the presence of multiple subcutaneous lipomata on the body and the extremities and an unsatisfactorily repaired right inguinal hernia.

The neurologic examination on admission to the hospital revealed the following: The cranial nerves were intact. The patient's gait was unsteady and he walked with a wide base. The Romberg test was positive. There was a slight tremor at rest of both hands, more on the right side. There was no dysmetria, but an action tremor developed on doing the finger-to-nose test. There was definite ataxia on doing the heel-to-knee test bilaterally. Muscle power was reduced in both lower extremities and in the right upper extremity. Muscle tone and volume were normal. Pain, temperature and touch were unimpaired. Vibration sense and position sense were impaired in both lower extremities. The deep and superficial reflexes were increased bilaterally in the upper extremities. The patellar and ankle reflexes were decreased. The abdominal reflexes were present. There were no abnormal reflexes.

Blood count (Oct. 12, 1944): 4,000,000 red blood cells, with 78% hemoglobin (color index 0.9); white blood cells, 10,400 (85% polymorphonuclears, 11% lymphocytes, 4% monocytes). Repeated blood counts showed nothing unusual in the appearance of the erythrocytes. The patient developed a pneumonia while in the hospital. After recovery the red blood cell count was 3,500,000 with a hemoglobin of 75% (C.I. 1.1).

Blood urea nitrogen was 18 mg. %. Fasting blood sugar was 62 mg. %. Urinalyses were repeatedly negative. Several blood Kolmer and Kline tests were negative.

Gastric analysis with histamine showed absence of free hydrochloric acid.

The cerebrospinal fluid was under normal pressure and the Queckenstedt test was negative. The protein was 41 mg. % and the serology was negative, as was the colloidal mastic test.

Roentgenogram of the vertebral column showed moderate thoracic scoliosis and some minor uncertain bony changes.

Two small subcutaneous nodules were removed for biopsy. Microscopic examination identified them as lipomata.

Liver therapy was started on the patient after he recovered from his pneumonia. He was given 3 cc. of Lederle's Liver Concentrate (15 U.S.P. units/cc.) 3 times a week. This was continued after discharge from the hospital and was increased to 3 cc. daily from February to April 1945. Since then it has been decreased until he is now taking 3 cc. twice a week.

The patient has shown progressive im-

provement. Some clinical evidence of nervous system disease still persists. Examination on May 20, 1946, showed the gait to be slightly unsteady (spastic-ataxic). This was more evident on turning and was increased with both eyes closed. The Romberg test was positive. Slight dysdiadokokinesia in the upper extremities and ataxia in the heel-to-knee tests were noted. Muscle power, tone and volume seemed good. Position and vibration sense were still a bit impaired in both lower extremities. Pain, touch and temperature perceptions were intact. The deep reflexes were increased in the upper extremities. The ankle jerks were absent. Knee jerks were present but fatigued easily. Hoffman signs were present bilaterally. Babinski's sign was not noted.

This man has returned to his work and does not find his remaining nervous system dysfunctions at all incapacitating.

**Discussion.** Before any genetic interpretations were made, it seemed advisable to establish the monozygosity of our patients beyond reasonable doubt. While there is no absolute method to determine this, Rife[11] has listed a number of criteria which may establish the zygosity of twins. These are: (1) the nature of the fetal membrane, (2) sex similarity, (3) physical resemblance, (4) blood types and subgroups, and (5) finger and palm prints. We could obtain no data as to the presence of monochorionic or dichorionic fetal membranes in our patients. They were of the same sex and their physical appearance was so identical that we often misidentified them. Their resemblance to each other in many physical details as outlined by Fischer[1] was so close as to leave little doubt of their similarity in this respect. Also of interest was the fact that they both had multiple subcutaneous tumors (lipomata), many of these occurring in relatively identical places on the body and of about the same size. Their father had similar nodules under his skin.

Blood studies were graciously done for us by Dr. Neva Abelson of the Philadelphia Serum Exchange at the Children's Hospital, Philadelphia. The twins' blood showed identical reactions. Both belonged to Group A1. The erythrocytes of both men reacted as follows: Anti-A1 positive; anti-N positive; anti-M positive; anti-Rho positive; anti-Rh′ positive; anti-Rh″ negative; anti-Hr′ positive.

Dr. David C. Rife, of Ohio State University, kindly studied the finger and palm prints of our 2 patients. He reported,[9] "The homolateral similarities are greater than the bilateral similarities of either. Each has a pattern in the thenar area in the left palm, while neither right palm shows a pattern in this area. The total ridge counts of the finger tips agree extremely well, F. W. having 91 and C. W. 92. This is close, even for twins. . . . the similarities are so striking that I feel reasonably certain that the twins must be identical."

On the basis of these criteria, we feel justified in concluding that our patients are really identical twins and are monozygotic.

Our patients did not show anemia or hyperchromic macrocytosis of the erythrocytes at any time. The clinical neurologic picture was that seen in posterolateral sclerosis. It is now well known that the neural symptoms of pernicious anemia may precede the hemic change. Under such circumstances the diagnosis depends on the clinical neurologic picture, negative laboratory and clinical studies implicating other known etiologic agents, the absence of free hydrochloric acid in the stomach after the subcutaneous administration of histamine and, finally, favorable therapeutic response to the parenteral administration of liver extract. Our patients fulfilled all of these criteria and we have concluded that the nervous system disease in these men was of the pernicious anemic type despite the lack of characteristic blood changes.

Certainly no final conclusion as to the hereditary basis of posterolateral sclerosis of pernicious anemia can be reached from our observations of this single set of identical twins. Yet we do feel that our cases added to those already recorded in the literature seriously suggest such a possible etiologic factor. Monozygotic twins are

genetically and physically more alike than other siblings or indeed any other 2 people. A non-infectious, non-contagious disease process occurring in one first and not long afterward in the other of a set of mon-oval twins certainly strongly suggests a possible common inherent basis for the disease process. Then when this disease is found to occur in ordinary siblings and other family relationships, the common inherent factor of the twins assumes hereditary features.

Genetic interpretation of posterolateral sclerosis is made more difficult by the many gaps in our knowledge of the causative factors and pathogenesis of the disease itself, and of the etiologic relationship of the condition to pernicious anemia. The idea that posterolateral sclerosis represents a toxi-infectious degeneration of the nervous system because of the absence of free hydrochloric acid in the stomach is no longer tenable. The old idea that the neural process is related to the anemia alone has long since been discarded. Most authorities today view the neural and hemic pathologic processes as a conditioned deficiency disease. Yet the etiologic relationship of pernicious anemia and subacute combined degeneration of the spinal cord still remains obscure. For instance, we do not know if the factor responsible for the integrity of hemopoiesis is the same as the factor responsible for the prevention of the development of status spongiosus in the nervous system so characteristic of posterolateral sclerosis. There may be 2 (or more) separate substances contained in the one therapeutic agent—liver extract. A definite chemical substance, folic acid, as a possible precise factor in the deficiency syndrome called pernicious anemia is only now being investigated. To date, we have seen no reports on the effect of this substance on the neural syndrome.

If different chemical substances are found and proven for the prevention of the hemic syndrome of pernicious anemia and for the prevention of the neural process of posterolateral sclerosis, the genetic problem might relate directly to these substances and their point of formation or use. Such a finding might well explain the greater incidence of the familial occurrence of pernicious anemia as Wilson so readily noted. It would mean that where familial pernicious anemia occurred alone, only the single hemic factor was disturbed on an hereditary basis; where familial posterolateral sclerosis occurred alone, only the neural factor would be involved; and where both pernicious anemia and posterolateral sclerosis were found to occur in a family, multiple hereditary factors would have to be postulated. On the other hand, if the hemic and neural factors are shown to be identical, the hereditary features of subacute combined degeneration of the spinal cord might have to be explained by some predisposition or susceptibility of the neural parenchyma itself. At this stage of our ignorance only fruitless, indecisive speculation can exist. All further genetic formulations would seem to depend on future observations on the etiology of these 2 conditions. However, we feel that wherever hereditary factors are found in pernicious anemia and/or in subacute combined degeneration of the spinal cord, such clinical studies should be added to the literature so that an eventual future genetic evaluation will be more sound and acceptable.

**Summary and Conclusion.** 1. Clinical and laboratory findings of identical twins with subacute combined degeneration of the spinal cord, gastric achlorhydria, and recovery with liver therapy are reported.

2. The monozygosity of the brothers was established on the basis of identical physical characteristics, blood groups, and finger and palm prints.

3. These cases are thought to strengthen the concept of heredity as one of the etiologic factors in the development of posterolateral sclerosis.

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# PROGRESS
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## MEDICINE

UNDER THE CHARGE OF

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## RENAL DECAPSULATION FOR OLIGURIA AND ANURIA

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SURGEONS who decapsulate kidneys in the expectation of increasing urinary flow usually justify themselves by assuming that the operation either diminishes intrarenal pressure or denervates renal bloodvessels. Other less plausible theories have been devised but these are the 2 most popular and of them the former is more widely held because of numerous clinical assertions that anuric kidneys often look swollen to the naked eye and that capsulotomy results in bulging of the renal parenchyma through the incision. Attractive as these theories may be in their simplicity, the actual basis upon which they rest seems slim indeed. Furthermore, it is so difficult to see how decapsulation can achieve anything approaching total denervation of the kidney that this review will confine itself to a consideration of the evidence that increased intrarenal pressure is an important factor in the production of the oliguric state.

It is conventional to deal with this problem by offering first a classification of the anurias. We are quite unable, however, to subdivide them in any satisfactory manner and, indeed, are prepared to suggest that no attempt to do so be made since it seems that diverse etiologic factors all produce anuria chiefly by the same fundamental mechanism; that is, increased tubular reabsorption of glomerular filtrate. Whether this broad generalization is strictly accurate or not, the familiar breakdown of the anuric phenomenon into: (*a*) *prerenal*, *renal* and *postrenal*, or (*b*) *glomerular* and *tubular varieties*, appears extravagant to us because a large variety of renal insults has been shown to initiate a series of events which culminates in apparently identical tubular lesions. Important as *prerenal* influences may be,[42,54,70] it is obviously not possible, for example, to diminish the rate of renal blood flow markedly without also affecting the nutritional status of the tubules, nor can the rate of glomerular filtration be appreciatively reduced without simultaneously offering the tubules a greater opportunity to exert their reabsorptive powers. By the same token *postrenal* obstruction is as certain to increase the rate of tubular reabsorption as it is to

diminish the minute output of glomerular filtrate. Since the volume of urine in the bladder is known to depend much more upon tubular than upon glomerular function, a brief summary of the effects of renal anoxia, nephrotoxic agents and obstruction of the lower urinary tract upon tubular structure and function may serve to justify this somewhat unitarian viewpoint and to place decapsulation in a proper perspective.

Effects of Renal Anoxia Upon the Tubules. No effort has been made to provide a complete bibliography of this relatively new but important field, but it is believed key references are included. Maegraith, Havard and Parsons[91] were apparently the first to attempt a unified explanation for the anuria which occasionally complicates a large and diverse number of prerenal conditions by suggesting that renal anoxia rather than hypothetical nephrotoxins or mechanical blockage of the tubules is the responsible agent. In an excellent review, Lucké[79] employs the term "lower nephron nephrosis" to describe the essentially similar degenerative lesions frequently found in conditions associated with destruction of tissue and intravascular hemolysis. He also emphasizes the importance of circulatory changes in the kidneys but believes that toxic chemicals and mechanical blockage of tubular lumens by protein precipitates may be contributing factors. His study, based upon 538 fatal cases accumulated by the Army Institute of Pathology, shows that essentially similar clinical and pathologic pictures of renal insufficiency have been produced by a large number of conditions—battle wounds and crushing injuries, abdominal operations, burns, transfusion reactions, sulfonamides, chemical poisons, heat stroke, blackwater fever, hemolytic anemias, obstetrical complications, acute pancreatitis and rickettsial diseases. The kidneys are described as usually swollen and somewhat enlarged; microscopically, the glomeruli seem relatively bloodless but otherwise normal, whereas the thick limbs of Henle's loops and the distal convoluted tubules show degenerative changes of variable degree and the lumens are here and there filled with pigmented casts. Interstitial edema, cellular infiltration and venous thromboses are also seen in the medullary portions of the kidneys. Interest in these lesions was originally aroused by the British descriptions of traumatic uremia and the "crush syndrome."[18,20,21,37,93]

By means of renal clearance technics it was soon shown that the application of a tourniquet to a dog's leg causes prompt reduction in renal blood flow and urinary output and that tubular function remains depressed for a considerable length of time after release of the tourniquet and disappearance of shock;[24c] but these authors noted no residual anatomic lesions in the kidney. Others, however, have described degenerative cellular changes in the kidney tubules following adequate mechanical constriction of the renal artery.[85,123,124] Phillips and co-workers[111] have shown that renal blood flow must be tremendously diminished before tubular function is impaired; but Corcoran and Page[24b] demonstrated that intense renal vasoconstriction does take place after skeletal injury. Lauson, Bradley and Cournand[75] have shown that in shock renal blood flow and glomerular filtration rate are reduced to a much greater extent than can be accounted for by the reduction in systemic arterial blood pressure, apparently as a compensatory effort on the part of the kidneys to counterbalance anoxia in other more vital organs. These authors agree with Corcoran and Page,[24b] and with Selkurt[124] that impairment of renal function may persist long after the circulatory disturbances elsewhere have been corrected.

Similar renal abnormalities have been described in conjunction with other kinds of circulatory disturbances—non-crushing injury,[30,104,107] hemorrhage,[24,24b,71,111,125] heat stroke,[92] burns,[14,56,100,127] obstetrical trauma,[11,101,106,149] sulfonamide intoxication,[51,52,80,97,110] incompatible blood transfusion,[2,9,28,32,33,44,79,91,114] retroplacental hemorrhage,[148] alkalosis,[83,87,99] diabetic coma,[82]

anemia,[10] pernicious anemia,[48] vomiting,[15] hematemesis,[7,157] Addison's disease,[133] enzyme shock[98] and congestive heart failure.[116,126,138]

These renal lesions have also been described in infectious diseases in which, although specific tubulo-toxins may be suspected, circulatory collapse is also common—cholera,[23] yellow fever,[41] and Weil's disease.[61] In blackwater fever similar episodes of renal failure frequently occur[50,51,88,89,90,137,142] as they may rarely in other hemolytic crises;[22,53,60,67,86,95] but here the possible toxic effects of hemoglobin derivatives can scarcely yet be separated from the circulatory changes. The part the pigments play will be discussed in the section on Nephrotoxins.

The "hepatorenal syndrome," a loosely defined combination of hepatic disease and renal failure, has been attributed on unproved grounds to the nephrotoxic action of hepatic substances.[143] It seems more likely, however, that no such syndrome exists and that the occasional case of renal failure associated with jaundice is due to circulatory changes resulting from shock, dehydration, anemia, chemical changes in the body fluid and infection, all of which factors may produce renal anoxia and artificial degeneration. There seems to be no reason to search for specific toxins.

Renal anoxia can hardly be supposed to play an uncomplicated rôle in glomerulonephritis, malignant hypertension and bilateral cortical necrosis of the kidneys where obstructive lesions in the glomeruli markedly reduce filtration rate and allow more complete reabsorption of tubular fluid.[24a,35,38]

Finally, extremely interesting observations have recently been made which, if confirmed, may explain the anurias of reflex or emotional origin. Trueta and his colleagues[5,135,136] have claimed that appropriate stimulation of peripheral nerves can divert the entire renal blood supply from its usual glomerular route directly to peritubular channels supplying only the medulla, the consequence being that glomerular filtration and urinary formation may partly or wholly cease without concomitant reduction in total renal blood flow. They regard this as a possible homeostatic mechanism which prevents loss of fluid (urine) from the kidney in conditions of shock and protects the glomerular apparatus from noxious agents. They feel that renal cortical ischemia can be produced centrally or peripherally through a variety of mechanisms, and that the different types of anuria just described may be of neurogenic origin. The implication is made that these anurias should be treated by spinal anesthesia or splanchnic block rather than by transfusion or decapsulation. These important claims should certainly be thoroughly explored, particularly since the reported experiments have been done only in rabbits which have an extremely labile glomerular system anyway. Barclay, Cooke and Kenney[4] have expressed skepticism about these claims, saying that changes in the cortical circulation are of relatively minor importance in the determination of urine volume in man. Wolf[145,146] has shown that pain itself can greatly diminish renal blood flow and suggests that diseased kidneys may not recover from such an insult. Cubitt[25] states that shock in the usually accepted sense is not a necessary precursor of the reflex anurias which may follow traumatic procedures. Although the mechanism of the anurias produced or accompanied by changes in the general circulation is not well understood, there is little evidence from these studies that increased intrarenal pressure is an important factor.

Effects of the Nephrotoxic Agents Upon the Tubules. The rôle which toxic products of tissue or blood destruction play in the production of renal insufficiency is far from clear. There is some evidence that circulating toxins appear in traumatic shock.[39,40,113] It was originally suggested that in "crush syndrome" degeneration of the distal convoluted tubules might result from precipitation of hematin in acid and concentrated tubular fluid,

and there seems to be no doubt that certain heme derivatives are cytotoxic.[24,24b] Flink[44] found that the amount of renal damage was proportional to the plasma hemoglobin concentration. Recent surveys, however, indicate that the excretion of hemoglobin derivatives is not the sole cause of tubular damage[50,79,91,147] and it is emphasized that these hemolytic disorders are often accompanied by circulatory disturbances which may involve the kidney to an important degree even though the superficial evidences of shock are not apparent.[30,88,107,134] Hemolytic crises have not been uncommon after the administration of certain sulfonamide derivatives;[49] but anuria may also be produced by mechanical blockage of the lower urinary tract with precipitated crystals. The effects of sulfonamide therapy on the urinary tract have been ably reviewed by Peterson and Finland.[110]

Hormonal influences have also been invoked as a cause of certain forms of oliguria. Brun and co-workers[16] have shown that the suppression of urine which follows prolonged standing is associated with the release of antidiuretic hormone into the blood stream. Bradley[10] suggests that the neurohypophysis becomes activated in hypoproteinemic states because of the loss of water into the tissues and consequent concentration of the plasma. Postoperative anuria may be due in part to hyperpitressinemia occasioned by peripheral sensory stimulation according to the mechanism of neurohypophyseal control described by Rydin and Verney.[121] Pitressin cannot properly be called a nephrotoxin, of course, but it does act upon the renal tubules to promote water absorption. The antidiuretic material detected in some edematous and oliguric states has not been absolutely identified as pitressin, however, and it should be remembered that the hormone cannot reduce urinary flow very much if the urine is already concentrated.[130] The importance of this type of oliguria, therefore, remains to be established.

Some heavy metals are known to be extremely toxic to renal tissue. Richards' direct observations on the frog's kidney[119] showed clearly that glomerular filtration (and presumably renal blood flow) was unaffected at the time that *mercury* had so damaged the tubules that the glomerular filtrate was being blindly and totally reabsorbed into the peritubular blood stream before it could leave the kidney. By means of clearance techniques it has also been shown that *uranium* can destroy tubular function without appreciatively affecting renal blood flow.[8] Page, Taylor and Kohlstaedt[102] have described the profound renal functional changes in *arsenic* poisoning. Forbes[46] found tubular degeneration in a case of *carbon tetrachloride* poisoning, as did Lucké,[79] who also includes cases of *mushroom* and *alcohol* poisoning in his "lower nephron nephrosis syndrome." In all these conditions oliguria is best explained by the reabsorption of glomerular filtrate through damaged tubular epithelium, and there seems to be no need of invoking swelling of the kidney to explain it.

Effects of Obstruction of the Lower Urinary Tract Upon the Tubules. It is conceivable that urinary formation may be impeded either by edema of the kidneys or by precipitation of material within the tubular lumens but there is little in the literature to suggest that either event occurs to such a degree as to raise intrarenal pressure above glomerular filtration pressure. Pathologists have evidently not been struck by any appreciable increase in the water content of anuric kidneys. This may be a postmortem artifact, but the observations of surgeons may also be deceptive since Culpepper and Martin[27] have noted that even gentle handling of the living dog's kidney results in an increase of intrarenal pressure measured directly. The matter of intrarenal pressure is discussed later; it is sufficient to say here that nothing is really known about the pressure exerted by interstitial edema in renal disease. Obstruction of the ureter or renal vein would certainly raise intrarenal pressure to an important

level but would not, of course, be logically treated by decapsulation.

It is also generally now thought that tubular obstruction by casts or precipitated pigment is a relatively unimportant factor in reducing urinary flow.[2,51,79,91] It has been repeatedly observed, for example, that spontaneous diuresis in these conditions is not accompanied by any outpouring of casts or cellular detritus. Except, therefore, for the rare instances of neoplastic or lymphomatous infiltration of the kidney, increased intrarenal pressure due to intratubular hydronephrosis appears to be an unimportant cause of anuria.

Intrarenal Pressure. Despite all the assertions that increased intrarenal pressure is an important etiologic factor in anuria, we have failed to discover any recorded instances in which this pressure has been measured. Neither have we found any reliable direct estimations of normal intrarenal pressure. Brodie[18] attempted to measure the general tension of the renal substance within the capsule during active diuresis but his technique was not described and his admittedly inaccurate results indicated a tension of about 40 mm. Hg, a figure which is almost certainly too high. Winton[144] made certain observations on isolated blood perfused kidneys of the dog which allowed him to calculate a hypothetical intrarenal pressure under those abnormal conditions. He found that a rise in ureteral pressure would fail to affect the urinary flow unless it exceeded a certain level, often about 10 mm. Hg. He attributed this to intrarenal pressure exerted laterally on some distal part of the tubules which kept them collapsed until they were forced open by urine under pressure just in excess of that in the renal tissue. Based upon that idea, indirect determinations of intrarenal pressure were made by measuring the ureteral pressure which must be exceeded to produce a perceptible fall in urinary flow. His figures varied from 4 to 14 mm. Hg, with a typical value of 10 mm. Hg. Winton states that decapsulation commonly halves this intrarenal pressure and that diuretics will elevate the pressure to 20 or 30 mm. Hg. From theoretical considerations of an "artificial nephron," Peters[108] states that an increase of a few millimeters of mercury in intrarenal pressure is sufficient to cause oliguria or anuria, predicts that bilateral decapsulation will reduce intrarenal pressure by about 50% and advises immediate operation whenever it is suspected that tubular dilatation, interstitial edema, inflammatory exudate, swelling of tubular epithelial cells, or invasive neoplasms may be causing intracapsular enlargement of the kidneys. Similar recommendations were made for the treatment of post-transfusion anuria,[109] but no statistics or case reports are offered.

Accurate measurement of the interstitial fluid pressure in the mammalian kidney is almost a technical impossibility because of its anatomic position and because bleeding results from the smallest puncture. One of us (W. S. C.) attempted to measure intrarenal pressure under various conditions by a method similar to that used by Henderson and associates,[62] Burch and Sodeman,[17] and Wells and coworkers[141] in their various studies on intramuscular, subcutaneous and intracutaneous pressures. The apparatus consists of a No. 22 needle with lateral openings, a calibrated adapter with 1 mm. bore containing isotonic sodium citrate, and a water manometer with rubber bulb attachment for varying the pressure upon the citrate column in the glass adapter. When the pressure in this system is raised, the intrarenal pressure is taken to be that at which the fluid column just begins to move into the tissue.

Preliminary acute experiments have shown this intrarenal pressure to be profoundly influenced by ureteral pressure, systemic blood pressure, venous pressure, the state of the renal arterioles, and induced diuresis. As previously stated, mere handling of the kidney in an anesthetized dog has produced the appearance of renal congestion, darkening

in color, and a rise in intrarenal pressure to a level about twice that of normal. In a small series of unanesthetized dogs with kidneys explanted to the lumbar region, Culpepper[26] also made repeated intrarenal pressure determinations through small nicks in the skin. Results varied in the normal animal from about 7 to 21 cm. of water with an average of about 16 cm. of water.

If it is assumed that increased intrarenal pressure may cause anuria, what is the mechanism of production? Does intrarenal pressure obstruct the outflow of blood or urine or of both? Stropeni[131] and Hülse and Litzner[68] have observed that decapsulation increases renal blood flow in dogs, but apparently no one has studied the matter in trained conscious animals by modern clearance techniques.

As for the possibility of intrarenal pressure obstructing the outflow of urine in the kidney, it can only be said that we do not know. However, Winton[144] is of the opinion that even in the normal kidney the intrarenal pressure is not an insignificant hindrance to urinary flow down the tubules; were the pressure removed entirely he believes the urinary flow would be 50 to 100% higher. Hence, it is not inconceivable that elevated intrarenal pressure from various causes may obstruct the outflow of both the blood and urine from the kidney, but until experimental studies of intrarenal pressure in anuric animals before and after decapsulation have been made, we shall not know whether decapsulation is indicated in the treatment of human anuria.

DECAPSULATION. The clinical reports of experiences with decapsulation are even less persuasive than the physiologic and pathologic observations. This is the situation possibly because no one reporter has had extensive experience but also because the protocols are usually incomplete, the diagnoses often uncertain, and the expected mortality rates under conservative management but crudely understood. It is certain too that failures are apt not to be recorded so that the statistics are heavily weighted in favor of surgical cures. We have examined the English literature over the past 20 years with the following results.

*Postoperative and Reflex Anuria.* Successful decapsulation for anuria following appendectomy in children has been reported 3 times.[47,65,66] Hyman[69] had the same experience in another child in whom anuria developed after multiple fractures and surgical correction. Muschat and coworkers,[98] and Hall[59] each reported a recovery from anuria following ureteral dilatation and cystoscopy, but Lowsley and Harbach[78] had 2 deaths under comparable circumstances.

*Crush Syndrome.* We found only 1 case report[84] and that patient died. Bywaters[19] states that when the syndrome is ordinarily recognized, one may expect only about one-third of the patients treated to recover.

*Postpartum Anuria, Including Cortical Necrosis.* Three successful experiences[23a, 74,112] must be contrasted with 4 fatalities.[31,72,101]

*Post-transfusion Anuria.* Eight recoveries have been reported by as many authors.[34,45,81,103,115,117,132,150] Prior to this, Beraud[6] reported a failure and Bancroft[3] a recovery. The mortality rate in this small group of cases certainly compares favorably with the overall mortality rate of 52% in the 200 cases collected by Hesse[64] and the similar mortality rates in reports of smaller series by Bordley,[9] Daniels and associates,[28] and Goldring and Graef.[55] It may be that these experiences lend support to the recommendations of Peters,[108] particularly if the operation is done early. The military experience in the last war has not yet been reported, but numerous personal communications suggest that it was not encouraging.

*Sulfonamide Nephrosis.* Although difficult to do so, we have tried to exclude those cases in which the anuria was apparently due wholly or in large part

to obstruction of the lower urinary tract by crystals. The cases are too few in number to be of great significance, but 6 successful cases of decapsulation for anuria associated with sulfonamide nephrosis[73,76,97,129,139,140] and 1 death[43] have been reported.

*Chemical Nephrosis.* Eight cases of mercuric chloride poisoning have been reported with 5 recoveries[12,63,105,118,122] and 3 deaths.[1,94,122] Recoveries following poisoning due to bismuth[151] and saponated cresol[77] were seen, but death followed operation in 1 case in which the anuria was attributed uncertainly to methyl alcohol.[128] The bichloride series is certainly not large enough to justify comparison with medically treated cases.

*Nephritis.* Although the rationale for treating glomerulonephritis is not clear to us, we have included 2 cases of patients who survived both the operation and the disease[36,58] and 3 who did not.[85a,120]

Thus, a total of 48 cases of anuria have been treated by decapsulation with a total mortality rate of about 32% (15 cases). Exactly half of these were subjected to unilateral operation only, and the mortality rate for this group of 24 cases was 16.6% (4 cases). Among the 24 cases in which both kidneys were decapsulated the mortality rate was 45.8% (11 cases).

It would, of course, be foolish to deny the possibility that interstitial edema contributes to the oliguric state, particularly in the face of descriptions like that of Reid, Penfold and Jones,[117] who decapsulated a pair of kidneys for post-transfusion anuria: "Both kidneys presented the same appearance: about twice the normal size, dark blue, and as firm as a tennis ball but less elastic. The capsules seemed very tense, a pale blue friable kidney bulged through the lines of incision owing to increased intracapsular pressure. The left kidney almost exploded and pieces of friable tissue were taken for microscopy." Directly opposed to this is a statement by O'Sullivan and Spitzer[101] who decapsulated kidneys in 2 cases of acute renal failure following abortion: "We could not convince ourselves that the kidneys in these cases were under tension at operation and we considered the operation tilted the scale rapidly against the patients." Consecutive case reports of post-transfusion anuria in the same issue of 1 journal arrive at contradictory conclusions; 1[103] attributes recovery to unilateral decapsulation, although 6 days after operation the blood urea nitrogen rose from 400 to 600 mg. per 100 cc., whereas the other[29] saw spontaneous diuresis on the 12th day with a blood urea nitrogen of 320 mg. per 100 cc. These citations illustrate the confusing clinical descriptions and emphasize the need for further experimental work.

**Conclusion.** Important as a large variety of prerenal influences may be in precipitating urinary suppression, the existing evidence favors the belief that the most important factor in maintaining the oliguric state is the appearance of tubular lesions which permit excessive reabsorption of glomerular filtrate. Little experimental, pathologic and clinical evidence has been found to support the belief that increased intrarenal pressure is a significant feature although it may be true that decapsulation has usually been performed too late.

A review of the literature on the subject in English for the past 20 years indicates that, with the possible exception of post-transfusion anuria decapsulation has not improved the recovery rate from anuria due to circulatory disturbances in the kidney or to toxic nephrosis. On the contrary, it suggests that if decapsulation is going to be done at all, it should be restricted to 1 kidney. Much experimental work is needed on the subject of intrarenal pressure. Until this is forthcoming, decapsulation of the kidney for the relief of anuria or oliguria must be regarded as an empirical therapeutic measure of unproved value.

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**Addendum.** Attention is called to a symposium published since this review was prepared. (**Bell, E. T.** and **Knutson, R. C.**: J. Am. Med. Ass'n., **134**, 441, 1947; **Corcoran, A. C.** and **Page, I. H.**: J. Am. Med. Ass'n., **134**, 436, 1947; **Martineau, P. C.** and **Hartman, F. W.**: J. Am. Med. Ass'n., **134**, 429, 1947; and **Moon, V. H.**: J. Am. Med. Ass'n., **134**, 425, 1947).

# NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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## ELECTROENCEPHALOGRAPHY

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When Newman[74] in 1938, in this same publication, reviewed the status of electroencephalography, the electroencephalograph had been in use in the United States for approximately 3 years. Since the first of January 1938 until July of 1946, 842 articles which are concerned with some aspect of electroencephalography are listed in the Cumulative Index Medicus. It is evident that a large amount of work has been done in this field and considerable progress has been made.

Today the electroencephalograph is firmly established as an accepted and reliable laboratory procedure. This has been accomplished in spite of the fact that its possible value, and especially the incidence of cortical dysrhythmia in certain conditions, has continued in unabated dispute. However, to such competent investigators as Dr. and Mrs. Gibbs, Jasper, Lennox, Robert Schwab, Kornmüller, Gray Walter, the Davis' and others, we owe the basic and sound principles of electroencephalography without which continued advancement would be impossible.

Unfortunately this examination is not available to many physicians in the United States. This was very evident in a recent unpublished survey made by one of us (F. G. E.) concerning graduate neuropsychiatric training in North America. It was surprising to find that many medical schools and institutions of good reputation have no functioning electroencephalograph laboratory. Many of these schools and hospitals stated that a laboratory would be set up if and when a trained electroencephalographer would join its staff; furthermore, there are many cities of approximately ½ million population or less which do not have this service and there are several states which have no electroencephalograph functioning within their boundaries.

Clinical Applications. To the practising physician the contribution of the electroencephalogram as a diagnostic aid in those patients complaining of seizures is one, if not the most important, of its uses in clinical medicine. Lennox[59] has estimated that at least 1 person in 200 (0.5% of the general population) in the United States have or have been subject to recurrent seizures. It is obvious that such a large group of severely handicapped individuals present an economic as well as hygienic problem to our nation. To accurately diagnose, treat and, perhaps, someday prevent the occurrence of epilepsy is directly concerned with electro-

encephalographic findings. It is generally accepted that between 80 and 90% of unselected adult epileptics will show evidence of cortical disturbance by electroencephalographic examination.[18,24,30,55] It is true that a rather large percentage of epileptics have a type of electroencephalographic abnormality which at present can only be regarded as a non-specific type of disturbance. Perhaps in the years to come these "non-specific" disturbances will be understood and used as a therapeutic guide. Until the work of Lennox,[58] the attempts to use the electroencephalogram as a therapeutic guide were very discouraging.

Lennox found a definite correlation between type of seizure, electroencephalographic abnormality and the therapeutic response to tridione. He describes these types of clinical seizures, which he calls pyknoepilepsy, myoclinic epilepsy and akinetic epilepsy. If patients with such seizures had electroencephalograms showing a 3 per second spike wave (Fig. 1 *C*) the therapeutic result following the administration of tridione was excellent. This electroencephalographic abnormality is a specific one, and has been referred to by Gibbs and Lennox as the "petit mal" type of dysrhythmia. Lennox also found that patients with similar clinical seizures, but with other types of electroencephalographic changes (Fig. 1 *D*) did not respond favorably to the administration of tridione.

Although epilepsy has always been thought to have an hereditary predisposition, it is amazing to find that the available information regarding this important subject is relatively meager. Again, Lennox and Gibbs[60] are the leading contributors. Their studies on monozygotic and dizygotic twins leaves little room for doubt as to the influence of heredity on the configuration of the brain wave pattern. A person may have an abnormal brain wave pattern without manifesting clinical seizures.[56] This individual, if the abnormality can be considered of cryptogenic origin, actually carries a predisposition to epilepsy. Lennox has arrived at several definite conclusions based on electroencephalographic findings which are concerned with the advisability of epileptics marrying and having children. He[57] states "The marriage of 2 normal persons who both carry a predisposition to seizures is worse than the union of an epileptic with a person who has no predisposition —a 'normal' person who carries a predisposition is as likely to have an epileptic offspring as an out and out epileptic." Lennox also believes that "the hereditary factor in epilepsy is about the same as in diabetes, one-half that in obesity and one-eighth that in migraine."

Many investigators[14,33,45,107] have studied the relationship of electroencephalography to post-traumatic epilepsy. Its value as a guide for surgical removal of the irritated area is of special importance.[79]

Penfield and Erickson,[80] working with Jasper, state that the presence of a 3 per second spike and wave (the petit mal pattern) practically rules out possible surgical intervention. However, the presence of focal electroencephalographic abnormality makes further investigation mandatory. As a rule, the post-traumatic epileptic is more apt to have a dysrhythmic electroencephalogram than is the patient with cryptogenic seizures. The post-traumatic epileptic is much more likely to have a focal disturbance (Fig. 1 *B*) but at times latent focal changes may pass undetected. Walker[102] has apparently partially solved this problem by studying the records of patients suspected of post-traumatic epilepsy during the injection of small amounts of metrazol. A previous latent abnormal focus is apt to appear, revealing the area of localized brain pathology.

Accurate information of the incidence of electroencephalographic changes in post-traumatic conditions has increased considerably.[8,15,33,35,36,41,53,54,76,79,80,95,100,105] This gain was largely at the expense of numerous service men injured in the line of dut

However, this new knowledge was put to good use and frequently, on the basis of an electroencephalogram, the disposition of a soldier was decided. The electroencephalogram was of particular importance in those individuals who had suffered a head injury and continued to have subjective complaints, but had no positive abnormal neurologic findings. The progressive improvement, the degree of abnormality, its presence or absence, were all used by the military physician in the evaluation of the post-traumatic condition. From Noell's[76] report it is obvious that the German military used this examination for similar purposes.

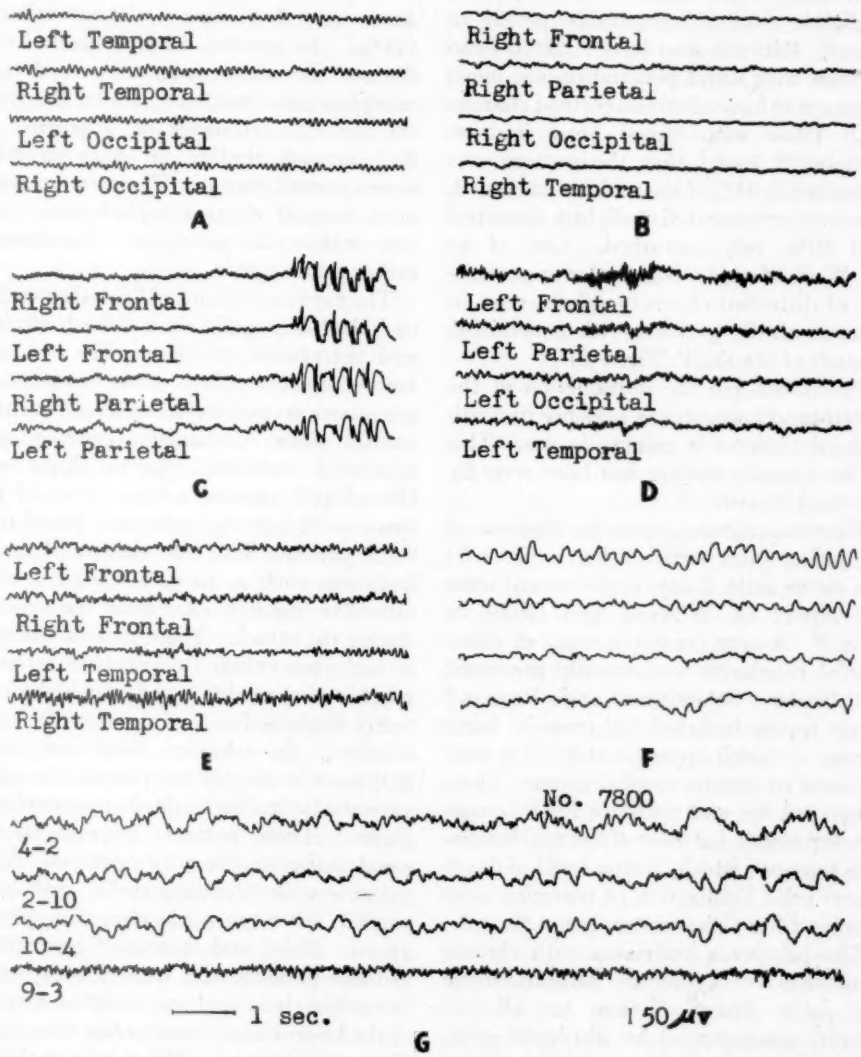


FIG. 1.—*Normal EEG'S.* *A*, 8.5 to 12 per second waves—alpha rhythm; *B*, low voltage fast * activity—beta rhythm. *Abnormal EEG'S.* *C*, Three per second spike and wave—petit mal type;* *D*, paroxysmal fast activity—grand mal type;* *E*, symptomatic epilepsy (focal abnormality in fourth channel, compare to third); *F*, slow waves following a severe head injury; *G*, phase reversal in a brain tumor.

* Terms used by Gibbs and Lennox.

It is evident that minor head injuries produced very transient changes in the electrical cortical activity.[15,105] In the severe head injuries, in those patients free of seizures, there frequently is a gradual improvement in the record up to 2 years after the injury. If the patient suffers from post-traumatic epilepsy, the improvement of the electroencephalogram is negligible over a comparable period of time.[33] Patients who have suffered head wounds with dural penetration are much more apt to have electrical cortical changes than those with closed head injuries. Williams[106] found that the pattern was disturbed in 94% of the patients examined. Kornmüller[53] found 37% slightly disturbed and 50% very disturbed. One of us (E. W. B.) found a slightly lower percentage of disturbed electroencephalograms in a series of 103 patients with penetrating wounds of the skull[8] (Fig. 1 *F*).

In civilian life the introduction of the electroencephalogram as evidence in medico-legal disputes is gaining in use. This rather complex subject has been recently reviewed by Gibbs.[32]

Electroencephalographic localization of expanding intracranial lesions (Fig. 1 *G*) has shown little, if any, improvement since the report by Williams and Gibbs in 1938.[108] A very extensive study of intracranial neoplasms was recently presented by Hoefer, Schlesinger and Pennes.[44] Their review included 543 cases of brain tumors of which approximately 70% were localized by electroencephalograms. Deep seated tumors and posterior fossa tumors are responsible for most of the non-localizable tumors. Smith, Walter and Laidlow[97] report good localization of posterior fossa neoplasm but this is certainly not the rule.

The psychoses associated with chronic alcoholism,[38,48] syphilis,[37] arteriosclerotic and senile brain[62] disease, are all frequently accompanied by disturbed cortical rhythms. Both the severity of clinical symptoms and the presence of symptomatic epilepsy directly affect the degree and incidence of electroencephalographic abnormality.

Liberson and Seguin[62] have observed in arteriosclerotic and senile mental patients a much higher percentage of abnormal electroencephalograms if the patient exhibits the clinical symptoms of confusion and marked irritability. Greenblatt and Levin[37] found double (90%) the incidence of abnormality in those patients with central nervous system syphilis and seizures as compared to those without seizures (44%). In general, in all organic brain disease the abnorma ity of the electroencephalogram tends to parallel the clinical findings. However, it is possible to find normal rhythm in patients with severe mental changes. The mere presence of a normal electroencephalogram does not make the psychosis "functional" rather than organic.

The vague complaint of "fainting spells" or "black-out spells" is a difficult clinical and therapeutic problem. The etiologic factors of short periods of unconsciousness are numerous and include a hypersensitive carotid sinus mechanism, epilepsy and hysterical reactions. Levin, Katz and Greenblatt[61] studied a large series of patients with fainting spells and found that some patients had true epileptoid manifestations such as an aura, tongue biting, muscular rigidity or clonic movements during the attack. These patients showed a high percentage of electroencephalographic abnormalities and should be correctly diagnosed as having minor epileptic seizures. In addition there are some patients who display no epileptic-like signs yet have typical epileptic electroencephalograms. These patients respond to the usual anti-convulsant medications. Most patients with "fainting spells" will have normal inter-syncopal electroencephalograms. Engel and Romano[82] report that in those patients with true vaso-depressor or carotid sinus syncope, a diffuse slowing of the brain waves accompanies the period of unconsciousness. They[22] believe that if the patient has a "fainting spell" during the electroencephalographic examination and no change in cortical rhythm is recorded, the spell can be classified as hysterical.

However, other investigators[25] have reported little or no change in cortical rhythm during carotid sinus syncope particularly of the "cerebral type."

Wilson's[109] concept that narcolepsy and epilepsy are etiologically similar has resulted in confusion in the minds of clinicians because the electroencephalograms of narcoleptics are frequently negative. Cohn and Cruvant[9] claimed to have found in narcoleptics "wave forms similar to those most commonly observed with the epileptics." Judging from the evidence they present, we do not feel that their conclusions are wholly justified. Dynes and Finley[16] in a study of 22 cases found no electroencephalographic abnormalities which would indicate a relationship to epilepsy. Blake, Gerard and Kleitman[4] expressed the opinion that normal sleep could be distinguished from narcoleptic sleep by the precipitous onset of sleep waves in the latter condition. It appears that, from an electroencephalographic standpoint, the only confirmatory evidence in the support of the diagnosis of narcolepsy rests upon the occurrence of a spell of uncontrollable sleep during the recording with an accompanying precipitous onset of sleep waves.

The medical literature concerned with the incidence and importance of disturbed electroencephalograms in behavior problem children, adult psychopathic personalities and criminals is confusing and filled with contradictions. Following the initial report of Jasper, Solomon and Bradley,[46] many authors have published electroencephalographic studies of children with behavior disorders and have found, according to their criteria, a high percentage of cortical dysrhythmias.[6,7,34,46,67,96] These percentages range upward to almost 90%. Some of the reports state that the abnormality most frequently found resembles or is identical with that encountered in epilepsy. However, Secunda and Finley[86] have expressed the opinion that the abnormality is an immature rhythm which is not commensurate with the patient's chronologic age. It has also been stated that enuresis, which reflects immaturity, is the only neurotic trait that occurs in positive association with abnormal electroencephalograms.[71,72] Based on the assumption that the disturbed cortical rhythm is in some way connected with the antisocial or undesirable behavior, drug therapy has been attempted and good results reported. Cutts and Jasper[10] reported beneficial results with benzedrine. Lindsley and Henry[68] agreed that benzedrine produced "strikingly improved behavior" and also found dilantin of value. The favorable behavior response following dilantin medication has been confirmed by others,[103] but all agree that phenobarbital should not be used and that no appreciable alteration can be observed in the electroencephalograms. Some people have reported an increase in the incidence of electroencephalographic abnormalities in behavior disorders or poorly adjusted children, yet are very cautious in their conclusions.[26,71,72,93] Solomon, Brown and Deutscher[93] commented: "Studies and results to date do not warrant further interpretation or clinical application in diagnosis, therapy or prognosis."

Jenkins and Pacella[47] agree that abnormal electroencephalograms are frequent in certain delinquency problems and they attribute this to an "organic" factor. They conclude that: "Electroencephalography does not contribute to the explanation of most cases of delinquency. Most instances of stealing, particularly group stealing and kindred activities, do not suggest the presence of an organic factor; rather, the contrary. These cases do not show a high incidence of abnormal EEG'S."

Numerous investigators[42,43,50,87,88,90] reported a high percentage of electroencephalographic abnormalities in persons diagnosed as a "psychopathic personality" and in criminals. Silverman[87,88] reports that 75 to 80% of criminal psychopaths have abnormal or borderline tracings. Gibbs, Bloomberg and Bagchi[28] in a preliminary report tended to support Silverman's findings. In the subsequent

publication[24] they corrected their evaluation of EEG normality with the factor of age and found no significant correlation between the EEG and the type of criminal behavior. They concluded: "Since the EEG is a fairly reliable indicator of epilepsy and organic brain disease, it seems reasonable to conclude that subclinical forms of these disorders are not contributing factors in a significant fraction of the 'sane' criminal population." In a study of persons diagnosed as constitutional psychopathic state in a military setting, Simon, O'Leary and Ryan[89] found a somewhat higher incidence of abnormal records than would be expected in a group of normal controls but were unable to find any relationship "between the severity of different manifestations of psychopathy and the incidence of abnormality in records."

The types of normal rhythms which occur in the psychoneurotic individual and the patient suffering from a functional psychosis is an intriguing but extremely complex subject which is difficult to evaluate. The complexity is aggravated by the numerous systems which have been employed in analyzing the records as to the preponderance, presence or deficiency of certain frequencies of brain waves. It is possible that more accurate and consistent results will be obtained with the use of an analyzer similar to that developed by Walter.[104]

Most of the electroencephalographers agree that beta waves, or low voltage fast activity, are more frequently found in excess in psychoneurotic individuals[5,94] than in a normal control group. However, a good or dominant alpha rhythm has been reported in patients with duodenal ulcers[43,83] and asthma[84] believed to be on a psychosomatic basis. Large amounts of beta activity (low voltage fast) and weak alpha rhythms are reported in schizophrenias, while a high incidence of manic-depressive patients are said to have a "strong" or "medium strength" alpha rhythm.[11,55]

Physiologic and Pathologic Investigations. In the last 9 years the most important advance in the interpretation and evaluation of electroencephalograms, in our opinion, centers upon the realization that the age of an adult is a factor which must always be considered when one speaks of a normal electroencephalogram. Berger,[3] Lindsley,[65,66] and Smith[91,92] reported the characteristics of the electroencephalograms of children and the normal progression from slow to faster activity which occurs from infancy to adulthood. Davis[12] observed the changes in cortical rhythm which accompany old age and Greenblatt[39] and Gibbs[29] reported that fast activity increases until the approximate age of 55, after which a decline in frequency is the expected trend. It was previously reported that the degree of slowing produced by hyperventilation is related to the patient's age.[31,63] This slowing is referred to by Gibbs as a "build-up" and the response of marked slowing or a "big build-up" decreases in frequency as the age of the subject advances.

The fluctuations of cortical rhythm which are produced by variations in blood sugar levels are now well known.[13,21] The misleading findings of increased slow waves which can result if a record is made after prolonged fasting are now avoided. Sensitivity to hyperventilation which accompanies hypoglycemia is expected and taken into consideration.[23,64] Attacks of spontaneous hypoglycemia[81] are accompanied by a slowing of the brain waves which definitely explains the mental symptoms and may have some diagnostic value. Strauss and Wechsler[98] have observed that psychoneurotics have "an unusual lability of the EEG to hyperventilation in the presence of normal blood sugar values." They also found a relationship between nervous complaints in the morning and the development of delta activity during hyperventilation in the fasting state.

Güttner and Bonkáló[40] reported that fatigue was accompanied by changes in cortical rhythm. Kornmüller[52] in his recent book described the appearance in the frontal lobes of choppy activity, poor

alpha rhythm and occasional slow waves in both acute and chronic fatigue states. Barnes and Brieger[2] examined 26 medical students and 1 professor "before the beginning of a typical day of classes and at the end of it." They failed to find any electroencephalographic change which could be considered evidence of mental fatigue. Kornmüller, at least in part, based his observations on the examination of aviators with flying fatigue which is not analogous to the condition of the medical students. Under any circumstances continued investigation is certainly justified.

Dynes[17] recently brought to attention the interesting previously observed phenomenon[69] that there is no distinct difference in the electroencephalogram of a person in a hypnotic trance and in the normal waking state. He points out that the hypnotic state is often spoken of as "an artificial sleep" or "sleep-like state." Just what hypnosis is, is still unexplained, but from the electroencephalographic findings it can be concluded that it is not a sleep variant.

Although there is no direct correlation between electroencephalographic abnormality and migraine,[95] an interesting electroencephalographic observation was made by Engel, Ferris and Romano. They had previously encountered, in a study of decompression sickness, a migraine-like syndrome.[20] Focal electroencephalographic abnormality was recorded during the scotoma of the migraine-like headache. Because of the similarity between this syndrome and true migraine, electroencephalograms were obtained on 3 subjects with migraine while experiencing scotomas. In all 3, abnormal electrical activity from 1 occipital cortex was demonstrated. This finding is evidence in favor of localized vasospasm which results in the scintillating scotoma.[19]

Electric shock, metrazol shock and insulin coma therapy all produced changes in the electrical rhythm of the cortex. Insulin treatment[49] results in a comparatively mild slowing of the rhythm, while metrazol[51] and electric shock[78] therapy produce more drastic changes. The degree of slowing, as would be expected, is influenced by the number of treatments and the time interval between each shock. Some patients seem to have a cortical rhythm which is resistant to change but this is a variable factor. The post-treatment abnormal electroencephalogram gradually returns to normal in a few weeks to a year after the termination of treatment. Some patient's electroencephalograms never return to normal, but a pre-shock EEG of such patients usually show evidence of a cortical dysrhythmia. Spontaneous convulsions have been reported following convulsive shock therapy. The 2 cases reported by Pacella and Barrera[77] had brain wave tracings prior to shock which were abnormal. It is probable that the treatment precipitated latent convulsive tendencies. Attempts have been made to correlate the pre- and post-shock electroencephalographic findings with clinical improvement, but the results have been of little value. One group[99] working entirely with schizophrenics found that the presence of an abnormal pre-shock tracing indicated a poor prognosis. A second group[1] which studied both schizophrenics and psychoneurotics were cautious in their conclusions, but felt that: "There is a suggestion that patients with pre-shock borderline-abnormal EEG's profit more as a group by shock treatment than those with normal EEG's."

Technical Considerations and the Future of Electroencephalography. During the past decade the manufacturers of electroencephalographs have improved their machines and undoubtedly will continue to do so with the return of critical material to civilian use. Repeated attempts have been made to devise a simpler method for applying the electrode to the scalp. Several mechanical methods which involve a headgear[70,101] have been developed as well as a clip-on electrode[75] and an adhesive non-drying electrode paste.[100] Only experience will prove whether or not

these techniques have any real advantage over the time-honored use of collodion applied electrodes.

Although the knowledge of electroencephalography has increased considerably, it has been somewhat hindered by lack of standardized techniques and uniform interpretation of electroencephalograms. Controversy has arisen over certain methods of frequency analysis and their validity. This is really a wholesome normal progression of events and is to be expected if advancement is to continue. During the year 1946 the formation of the Eastern Association of Electroencephalographers was a definite step forward and provided the much needed opportunity for group discussion. The recent organization of the American Society of Electroencephalographers may provide this and other advantages to the electroencephalographers throughout America.

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# BOOK REVIEWS AND NOTICES

DIAGNOSIS IN STERILITY. Proceedings of Conference Sponsored by The National Committee on Maternal Health, Jan. 26–27, 1945, New York City. Edited by EARL T. ENGLE. Pp. 237. Springfield, Ill.: Charles C Thomas, 1946. Price, $5.00.

THIS volume assembles in a very readable form a considerable amount of the current thinking upon the problems encountered in the investigation of infertile couples. Its contributors are experts in their respective fields. The chapters on semen analysis are very informative. Each chapter in the book includes a discussion by various members of the conference, and the papers are all ably and interestingly summarized by Dr. Rock. The volume of necessity does not cover completely all aspects of the subject. It would have been of considerable interest if a paper had been included upon the timing of ovulation as recently reported elsewhere by Farris. In spite of the limited field of topics presented at the conference, the volume is well worth the attention of everyone concerned in the treatment of human infertility. D. M.

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EXPERIMENTAL HYPERTENSION. By WILLIAM GOLDRING, RICHARD J. BING, EDUARDO CRUZ COKE, W. D. COLLINGS, L. W. DONALDSON, M. L. GOLDBERG, HARRY GOLDBLATT, B. GOMBERG, ARTHUR GROLLMAN, C. A. JOHNSON, OLIVER KAMM, LUIS F. LELOIR, H. MINATOYA, W. G. MOSS, ERIC OGDEN, IRVINE H. PAGE, JOHN W. REMINGTON, L. A. SAPIRSTEIN and G. E. WAKERLIN. Being the Results of a Conference on This Subject Held by the Section of Biology, of The New York Academy of Sciences, Feb. 9 and 10, 1945, New York City. Pp. 179; 60 ills. New York: New York Academy of Sciences, 1946. Price, $3.75.

THIS timely monograph deals primarily with recent advances in the study of humoral and chemical factors in clinical hypertension, and the renal type of experimental hypertension. It is tersely written, with appropriate introductions, summaries, illustrations and bibliographies. For one wishing to bring himself up-to-date in this field it will make most profitable reading. W. J.

A TEXT BOOK OF CLINICAL NEUROLOGY. By J. M. NIELSEN, B.S., M.D., F.A.C.P., Associate Clinical Professor of Medicine (Neurology), Univ. of Southern California; Senior Attending Physician (Neurology), Los Angeles County General Hospital. 2nd ed. Pp. 699; 190 ills. New York: Paul B. Hoeber, 1946. Price, $7.50.

THE 2nd edition of this excellent textbook embodies the advances occurring in the 5 years elapsing since the 1st edition. The sections on electroencephalography, the physiology of the basal ganglia and cerebral cortex, and the use of the sulfonamides have been revised, and new sections on toxoplasmosis, the use of penicillin in neurologic diseases, and the syndrome of neuromuscular exhaustion have been added. The author's style is lucid, and the presentations of the subject matter clear and concise. He incorporates his extensive personal experience, rather than presenting merely a warmed-over compilation of the literature. The book is highly recommended both for students and general practitioners, while specialists in the field will find it interesting reading. C. R.

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SOME CHAPTERS IN CAMBRIDGE MEDICAL HISTORY. By SIR WALTER LANGDON-BROWN, Emeritus Professor of Physic in the University of Cambridge. Pp. 119. Cambridge: at the University Press; New York: Macmillan, 1946. Price, $1.75.

BASED on a series of lectures to the Royal Society of Medicine, this account of Cambridge medical history extends over 4 centuries. It emphasizes Carlyle's dictum that "history is the shadow cast by a few great men." Thus, there are considered such men as Caius, Gilbert, Glisson, Heberden, Haviland, Paget, Humphrey, Foster and Allbutt. They are used in turn to illustrate the Revival of Learning, the Dawn of Experiment, the Insurgent Century, the Age of Reason, the Beginning of Reform, the Rise of the Medical School, and the Transition from the Nineteenth Century. To those who have seen the summaries of these lectures in the *Proceedings* of the Royal Society of Medicine, and who heard with regret of the passing of their cultured and

philanthropic author, this more concrete form of the material is welcome; for medical Cantabrigians it should furnish a useful record; to almost any intelligent person it should provide pleasant and profitable reading.

This is a book for a larger public than its title seems to invite, not only because of the good selection of subject matter, which touches on far more than Cambridge medicine, but because of the author's entertaining style. E. K.

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HUMAN GENETICS. By REGINALD RUGGLES GATES, B.Sc., PH.D., M.A., LL.D., Fellow of the Royal Society; Emeritus Professor of Botany, Univ. of London; Hon. Chairman, Bureau of Human Heredity; Past Vice-President of the Eugenics Society, the Royal Anthropological Institute, the Linnean Society; Past President of the Royal Microscopical Society; sometime Associate Professor of Zoology, Univ. of California. 2 vols. Pp. 1518; 326 ills. New York: Macmillan, 1946. Price, $15.00.

THIS book is intended as a survey of modern developments in the field of human heredity. Though written from the point of view of a biologist, much of it deals with subjects of great medical importance. The scepticism of many physicians in regard to the findings of the geneticists may be due partly to the experimental basis of the science, largely a study of heredity in plants and lower animals. It is only in recent years that human genetics, proceeding necessarily by analogy rather than experiment, has acquired a large body of knowledge.

For broad scope and clear presentation of an immense amount of detail this book by Gates is unique in its field. Here one can easily find material dealing with practically every hereditary variation and abnormality that has been described. Though much of the discussion is interspersed with lengthy citations of work done on lower forms, these asides are quite relevant in that they demonstrate the types of material from which theories of human heredity are derived.

The first volume deals chiefly with the heredity of variations and abnormalities of organs and organ systems. General principles of heredity in man are rather briefly treated, an elementary knowledge of genetics being assumed. A chapter is devoted to eye and hair color, another to color blindness, a third to disorders of the skeletal system. Other systems are considered in a similar manner. The heredity of the blood groups, very actively investigated in recent years, is given an excellent and up-to-date presentation.

In the second volume such topics as allergy, cancer, susceptibility to disease, hereditary syndromes and anthropologic characters are taken up. The reader will find many controversial points on which the author gives rather summary opinions. These range from cases where there is actual question of whether a disorder is inherited or not, *e. g.*, Hodgkin's disease, to the finer points of genetics such as the use of the concept of "penetrance." Anyone desiring further information will be greatly aided by the hundreds of well-annotated references at the end of each chapter.

The paper is a fairly good war time product, the printing and the charts very clear. Genetic symbolism adopted by the Federation of Eugenic Organizations is used throughout. The relatively few photographs are for the most part reproductions, and, though of only fair quality, illustrate the various conditions sufficiently well.

The author is to be congratulated for assembling this most complete reference work on an important and neglected subject, and particularly for providing the interested physician with a key to its vast literature.

C. B.

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NEW ASPECTS OF JOHN AND WILLIAM HUNTER. By JANE M. OPPENHEIMER, Bryn Mawr College. Foreword by FENWICK BEEKMAN. Pp. 188; 5 ills. New York: Henry Schuman. Price, $6.00.

To the large body of Hunteriana a skilful writer here adds 2 essays—"Everard Home and the Destruction of the John Hunter Manuscripts" and "William Hunter and His Contemporaries." Working as a Guggenheim Fellow at Yale and then at Bryn Mawr College, she has culled from the mass of the data sufficient evidence to show that though Home behaved unwisely "his actions were not those of a guilty man." Nor does she believe him guilty—rather that he foolishly omitted formal acknowledgment of his debt to "the powerful little man of five foot two who dominated medical science in

his century." "In Great Britain" should have been added.

Of William Hunter's less important career, Miss Oppenheimer selects a comparatively unknown side—his meddling in politics and his contacts with Queen Charlotte, Pitt, Walpole and others of the aristocracy. Neither aspect, however, appears to be either edifying or entertaining, though both confirm the estimate of his narrow fallibility—his "skew path to imagined power" and "a willingness to compromise his integrity" that was the antithesis of the nature of his greater younger brother. E. K.

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PRINCIPLES IN ROENTGEN STUDY OF THE CHEST. By WILLIAM SNOW, M.D., Director of Radiology, Bronx Hospital, Roentgenologist in Charge, Harlem Hospital, New York. Pp. 414; 508 ills. Springfield, Ill.: Charles C Thomas, 1946. Price, $10.00.

THIS is another book on the chest which explores a phase slightly different from conventional texts. It is not an atlas and it is not a text. The descriptions of lesions are given in a short and abbreviated style very much as one would prepare an abstract. Many of the physiologic and pathologic considerations have been completely omitted. The author has not attempted to consider many of the excellent contributions to the study of chest diagnosis. He does consider bronchial spasm, carbon dioxide tension, and lung circulation briefly but almost excludes considerations of the dynamics of the lung, about which so much has been written and which is so important in the consideration of any interpretation of lung lesions.

As one reads the text the lack of reference material is felt. The illustrations, some of which are good and some poor, have inadequate legends and the majority have no history. One feels the need for illustrations made in views other than many of those included in the publication. The lack of emphasis on differential diagnosis is apparent throughout.

The arrangement of the illustrations in this book is most unusual. Some are arranged symmetrically and are pleasing to the eye and others are off-set, protruding into the margin, and the legends are not well placed. The index does not refer to any of the illustrations but merely refers to the subject matter; on turning to the subject matter one may find no reference to any illustrations of relatively well-known and common lesions.

The publisher as usual has provided excellent paper for his book and the print is pleasing to the eye. The illustrations of good negatives are excellent, but there are a number of illustrations which do not show the lesion that the author intended to demonstrate and this is in spite of the fact that both space and size of illustrations are adequate. E. P.

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